HOSS Bank

This is a compilation of answers for the MCh theory exit exam from recent papers. We do not claim originality or copyright of any of the material. We are evergrateful to our teachers who relentlessly taught us Urology and inspired to read more. We hope these notes will be as useful to you as they were to us.

Heman P

Onkar S

Santhosh N

Sudhindra J

Basic science/ misc

1. Urinalysis

- **Urine collection**
  - Best/Ideal/Gold Standard method (in both males & females)→ Suprapubic aspiration
  - Best practical method in **males**→ Midstream urine (MSU) collection
  - Best practical method in **females**→ Per-urethral catheterization and mid-catheter urine (MCU)
  - Best method in neonates & infants→ IFT sample
- All urine samples should be examined **within 1 hour** of collection
- Urine samples should be refrigerated at 5° C, and should be cultured within 24 hours of refrigeration.
- **Specimen of choice** (for evaluation of UTI, GUTB)→ First morning sample

A. **Physical Examination of Urine:** includes an evaluation of color, turbidity, specific gravity and osmolality, and pH.

1. **Abnormal colour of urine**

1	**Yellow**	Normal, Phenacetin, Riboflavin/flavins
2	**Red**	Hematuria, Hb-uria/Myoglobinuria, Phenothiazines, Rifampicin, Phenolphthalein (in bowel evacuants), Chronic Pb & Hg poisoning, Beets & Blackberries (Anthrocyanin)
3	**Orange**	Dehydration, Pyridium, Sulfasalazine
4	**Green blue**	Biliverdin, Amitriptyline, Methylene-blue, Indicanuria, Indigo carmine, Phenols, I/V Promethazine (Phenergan), Triamterene
5	**Brown**	Urobilinogen, Nitrofurantoin, Metronidazole, Porphyria, Furazolidone, Chloroquine & Primaquine, Aloe-vera, Fava beans, Rhubarb
6	**Brown-black**	Alcaptonuria, Melanin, Hemorrhage, Tyrosinosis, Methyldopa, Cascara, Senna (Laxatives)

2. **Cloudy/Milky urine**→ Phosphaturia **(**MCC), Pyuria, Chyluria, Lipiduria, Hyperoxaluria, Hyperuricosuria
3. **Specific gravity of urine**
   - Varies from (range)= 1.001- 1.035
   - Average= 1.010- 1.020
   - Indicates state of hydration
   - Specific gravity less than 1.008 is regarded as dilute
   - Fixed specific gravity of 1.010 is a sign of renal insufficiency
   - Dipstick measurement of specific gravity is NOT reliable
   - **Conditions that decrease specific gravity**
     - Increased fluid intake
     - Diuretics
     - Decreased renal concentrating ability
     - Diabetes insipidus (DI)
   - **Conditions that increase specific gravity**
     - Decreased fluid intake
     - Dehydration (Fever, sweating, vomiting, diarrhea)
     - Diabetes mellitus (Glucosuria)
     - SIADH
     - After IV injection of iodinated contrast & in patients taking dextran [May be even > 1.035]
4. **Osmolality of urine**
   - Varies from (range)= 50- 1200 mOsm/L
   - Most commonly varies with hydration
   - Urine osmolality is a better indicator of renal function than osmolality
   - Same factors that affect specific gravity also affect osmolality
   - Cannot be measured by dipstick
5. **pH of urine**
   - Varies from (range)= 4.5-8
   - Average= 5.5-6.5
   - pH between 4.5 and 5.5→ Acidic urine
   - pH between 6.5 and 8→ Alkaline urine
   - In general, urinary pH reflects the pH of the serum
     - In metabolic/respiratory acidosis→ urine is acidic
     - In metabolic/respiratory alkalosis→ urine is alkaline

RTA is an exception to the above general rule. In RTA urine does not become acidic (i.e. inability to acidify urine below a pH of 5.5) after an acid load→ **Diagnostic of RTA**

B. Chemical Examination of Urine (Dipstick)

1. **Urinary dipstick testing-** abnormal substances commonly tested:

S. No.	Substance	Basis of test	Additional facts
1	Hematuria	Peroxidase activity of Hb	➢ Sensitivity (>3BRCs/HPF)= >90%, Specificity is lower ➢ Normal individual excretes about 1000 RBCs/mL of urine [Upper limit of normal is 5000-8000 RBCs/mL] ➢ **FP-** High specific gravity urine (Dehydration, Exercise, First morning sample), Contamination with menstrual blood- most often
2	Protein	Tetra-bromophenol (TBP) blue dye test	➢ Colour changes to 'Blue' ➢ Detects **albumin only** ➢ **FN-** Alkaline urine, Dilute urine (detects only when protein conc. >20-30 mg/dL), When primary excreted protein is not albumin
3	Glucose	Double oxidation (oxidase-peroxidase) reaction	➢ Specific for **glucose only** ➢ Renal threshold for glucose 180 mg/dL ➢ **FN-** Ascorbic acid
4	Ketones	Na-nitroprusside test	➢ Colour changes to 'Purple' ➢ Detects **aceto-acitic acid only** ➢ Ketones excreted in urine when fat breakdown occurs during depletion of carbohydrate supply e.g. DKA, pregnancy, starvation, rapid weight reduction. ➢ With abnormal fat breakdown, ketones appear in urine before the serum ➢ Ketones excreted include- Acetoacetic acid (AAA), Acetone, β-hydroxybutyric acid (HBA) ➢ **FP-** Acidic urine of high specific gravity, Abnormally colored urine, Urine containing levodopa metabolites, 2-mercaptoethane sulfonate- Na, and other sulfhydryl containing compounds
5	Bilirubin & Urobilinogen	Diazonium salt reaction	➢ Normal urine: Bilirubin- absent, Urobilinogen- small amount ➢ Only in pathologic conditions, bilirubin (only conjugated) may be present in urine. ➢ Unconjugated bilirubin NEVER appears in urine even in pathologic conditions. ➢ **FN-** Ascorbic acid ➢ **FP-** Pyridium
6	Pyuria (WBCs)	Leucocyte esterase (LE) test	➢ LE mainly produced by neutrophils ➢ LE converts indoxyl carbonic acid to indoxyl which in turn changes the color of the indicator agent ➢ **FN-** Ascorbic acid, Old sample, High specific gravity, Glycosuria, Urobilinogen in urine, Drugs that alter urine color ➢ **FP-** Contaminated sample
7	Bacteria	Nitrite test (Diazotization of dipstick reagent to form red azo dye)	➢ Colour changes to 'Red' ➢ Nitrites normally NOT present in urine ➢ Sensitivity= 35-80%, Specificity= >90% ➢ **FP-** Contaminated sample

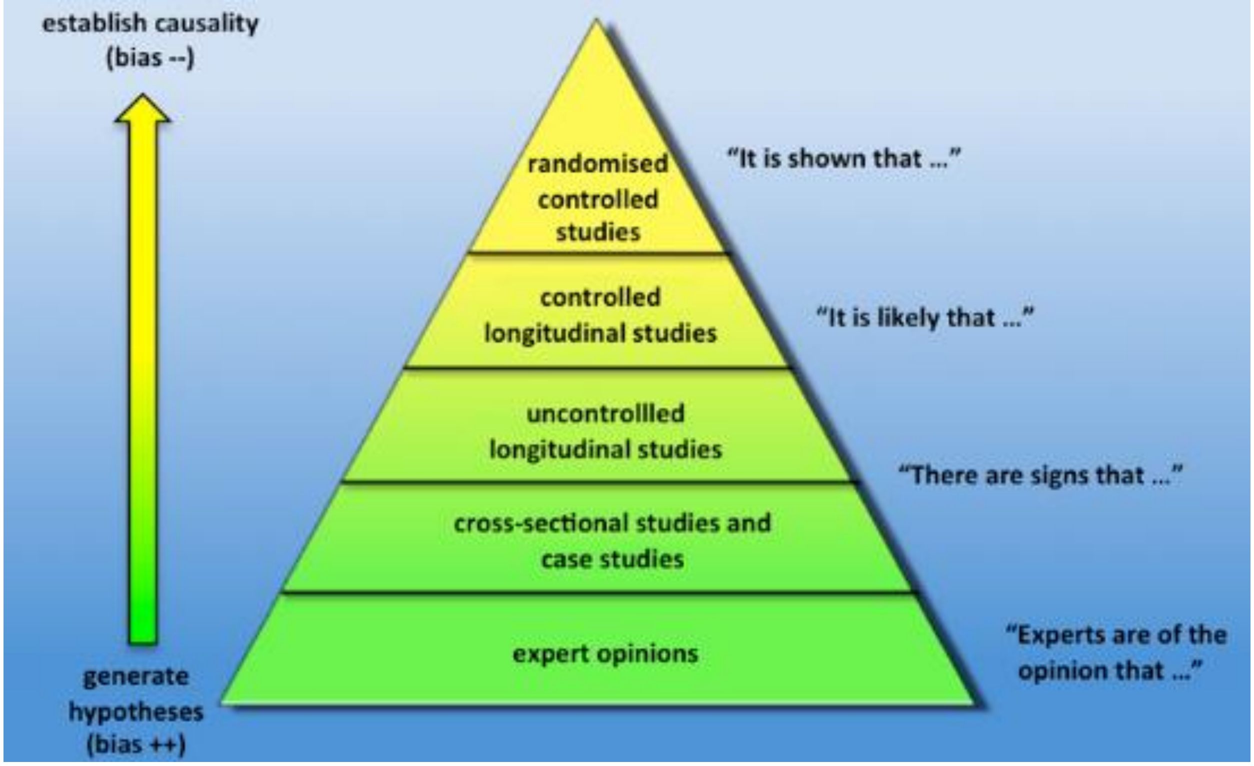
C. Microscopy

- Preparation of sample→ 10-15 ml urine is centrifuged (at 3000 rpm for 5 min). Supernatant is discarded and sediment resuspended and then examined on a slide under:
  - **Low-power→** (1) Cells [RBCs, WBCs, Oval fat macrophages], (2) Casts, (3) Cystine crystals, (4) Parasites
  - **High-power→** (1) Bacteria, (2) Yeast, (3) Crystals other than cystine, (4) To distinguish circular from dysmorphic RBCs (RBC morphology)

2. Levels of evidence

Given by 'Oxford Centre for Evidence-based Medicine' (Oxford CEBM) in 2009 and modified in 2011

Level of evidence		**Description**	**Grade of recommendation**
I	Ia	Evidence from a systematic review (SR) or meta-analysis of RCTs or evidence-based clinical practice guidelines based on systematic reviews of RCTs. Evidence from three or more RCTs of good quality	A
	Ib	At least one well-designed RCT (e.g. large multi-site RCT) with narrow CI	
	Ic	All or none randomized controlled trials	
II	IIa	SR of cohort studies	B
	IIb	Individual cohort study or low quality RCTs or well-designed non-RCTs	
	IIc	Outcomes Research studies- ecological studies	
III	IIIa	SR of case-control studies	
	IIIb	Individual case-control study	
IV		Poor quality cohort and case-control studies	C
V		Expert opinion without explicit critical appraisal, or research	D



3. Oncogenes

- Oncogenes: mutated form of normal genes (proto-oncogenes)
- Positively associated with cellular proliferation
- Two common oncogenes over-expressed in various cancers: *MYC* and *MET*
- Others: *ERBB*
- Proto-oncogene *MYC*

  - Encodes an early-response transcription factor that regulates cellular proliferation. Amplifcation of *MYC* is commonly found in prostate cancer. Expression of *MYC* in prostate epithelial cells leads to immortalization.
  - Increased expression of *MET* has been reported in RCC and is more frequent in higher grade cancers. Hepatocyte growth factor (HGF) acts through a receptor that is encoded by *MET gene.*
  - Mutations of *MET* proto-oncogene are also associated with hereditary RCC.
- Mechanisms by which proto-oncogene can be converted to an activated oncogene:
  1. Mutation of the proto-oncogene resulting in an active form of the gene product
     - Mutation in proto-oncogene gene can lead to a continuous proliferation signal. E.g. mutation of the proto-oncogene ***ERBB***, which encodes for the epidermal growth factor receptor (EGFR), results in expression of a receptor that is constitutively active.
  2. Gene amplification
     - Gene amplifcation and aneuploidy (increase in the number of copies of a gene) may occur during chromosomal replication. This results in increased number of mRNA transcripts and overproduction of the corresponding protein. E.g. this is the underlyning mechanism in overexpression of ***MYC*** in some types of bladder cancers that is found in more than 50% of papillary and invasive bladder tumors.
  3. Chromosomal rearrangement
     - Chromosomal translocation events can result in the formation of an oncogene e.g. **fusion of a portion of *TMPRSS2* gene and *ERG*** oncogene in majority of prostate cancers.

4. Tissue engineering

- Tissue engineering has an important role in achieving the goals in regenerative medicine which include the replacement of damaged, injured, or missing body tissues with biologic-compatible substitutes.
- Advances in tissue engineering techniques, use of newer and smart biomaterials and new techniques for vascularization allow more complex organs to be engineered
- Nonseeded matrices can fill a defects up to 1 cm
- Cell-seeded matrices for defects larger than 1 cm
- Three classes of biomaterials have been used for engineering of genitourinary tissues:
  - Collagen and alginate
  - Acellular tissue matrices-bladder submucosa and small-intestinal submucosa
  - Synthetic polymers-polyglycolic acid (PGA), polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA)
- Vascularization
  - Limiting factor for the engineering of tissues is that cells cannot be implanted in volumes exceeding 3 mm3
  - Nutrition and gas exchange are limited by this maximal diffusion distance. If cells were implanted in volumes exceeding 3 mm3, only the cells on the surface would survive, and the central cell core would undergo necrosis resulting from a lack of vascularity.
  - Three approaches have been used for vascularization of bioengineered tissue
    1. i. Use of angiogenic factors in the bioengineered tissue
    2. ii. Seeding embryonic cells with other cell types in the bioengineered tissue
    3. iii. Prevascularization of the matrix before cell seeding

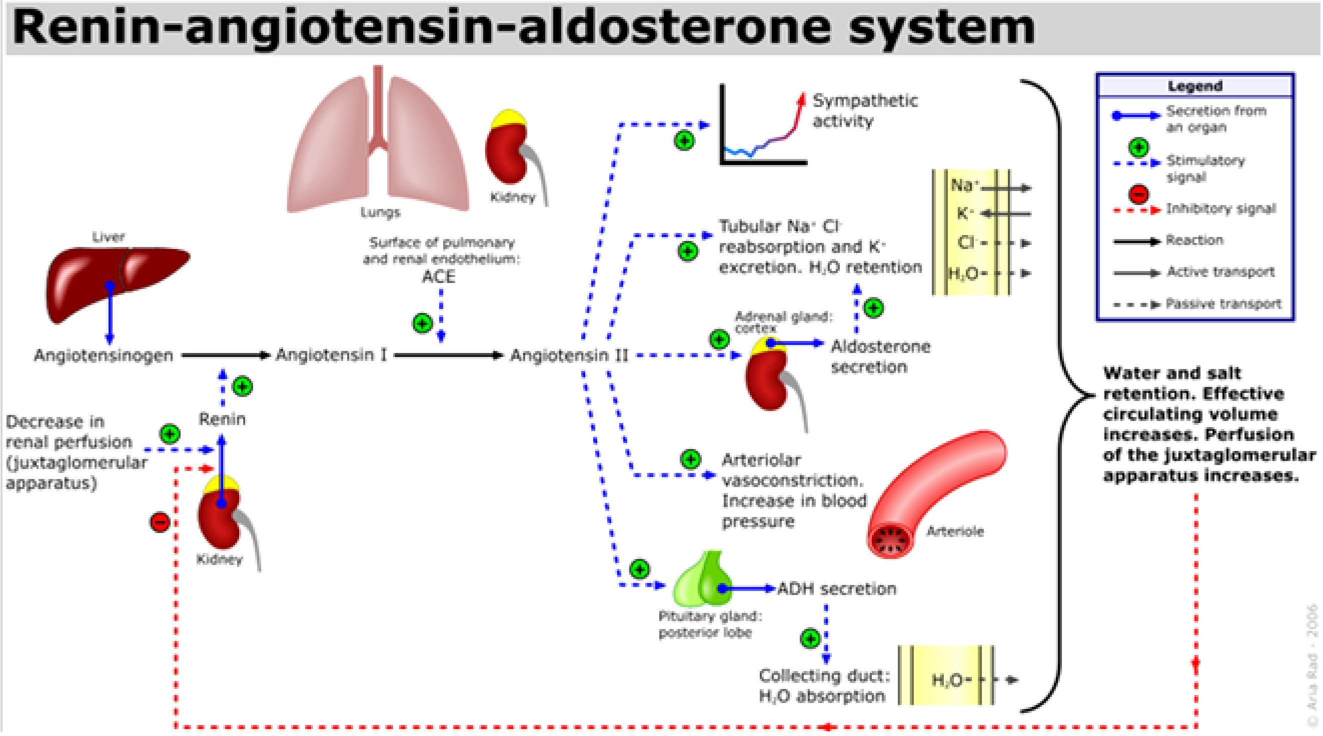
- Sources of cells for tissue engineering

Stem cell	Advantages	Disadvantages
Embryonic	Pluri-potent	▪ Trans-differentiate to malignancy ▪ Require immune-suppression ▪ Ethical issues
Adult	Not pluri-potent	▪ Do not trans-differentiate ▪ Slower rate of replication ▪ No ethical issues
Fetal	Multi-potent	▪ Do not trans-differentiate ▪ No ethical issues

- **Applications of tissue engineering in urology**
  1) **Urethra:** For failed hypospadias reconstruction, Long recurrent and/or complex urethral stricture, long PFUDD
     - Bladder acellular collagen matrices, nonseeded small intestinal submucosa (SIS), collagen matrices have been used
  2) Bladder regenration: Both synthetic and organic materials have been used in experimental and clinical settings for bladder wall regeneration.
     - Synthetic materials→ Polyvinyl sponge, Teflon, collagen matrices, Vicryl (PGA) matrices, and silicone. These materials failed because of mechanical, structural, functional, or biocompatibility problems.
     - Organic material→
       - Nonseeded allogeneic acellular bladder matrices
       - Cell-seeded allogeneic acellular bladder matrices
       - SIS
     - Selective cell transplantation may provide a means to create functional new bladder segments
  3) Bladder cell therapies: Applied to treatment of urinary incontinence, regeneration of injured striated urethral sphincter and vesicoureteral reflux
  4) Reconstruction of penile urethra
  5) Possible ole in treatment of erectile dysfunction
  6) Vaginal recnstruction
  7) Regeneration of renal tissue

5. Renin Angiotensin Aldosterone system (RAAS)

- RAAS plays a fundamental role in maintaining blood pressure and extracellular volume.
- RAAS is composed of a series of proteins and peptides that react and result in a series of actions. Several organ systems have their own local RAAS.
- Primary role of the RAAS is to maintain tissue perfusion, especially in cases of hypovolemia.


Renin-angiotensin-aldosterone system
Lungs
Kidney
Liver
Surface of pulmonary and renal endothelium:
ACE
Angiotensinogen
Angiotensin I
Angiotensin II
Renin
Decrease in renal perfusion (juxtaglomerular apparatus)
Kidney
Sympathetic activity
Tubular Na+ Cl- reabsorption and K+ excretion. H2O retention
Na+
K+
Cl-
H2O
Adrenal gland: cortex
Aldosterone secretion
Arteriolar vasoconstriction. Increase in blood pressure
Arteriole
Pituitary gland: posterior lobe
ADH secretion
Collecting duct: H2O absorption
H2O
Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Legend
Secretion from an organ
Stimulatory signal
Inhibitory signal
Reaction
Active transport
Passive transport
© Aria Rad - 2006

- **Main components:**
  - Angiotensinogen
  - Renin
  - ACE
  - Angiotensins

- **Angiotensinogen**
    - It functions as a serine protease inhibitor
    - Liver is the primary site of synthesis
- **Renin**
    - Secreted from JG cells of afferent arteriole
    - Kidney is major site of synthesis
    - **Renin secretion is stimulation by**:
        - Reduction of distal tubule salt delivery
        - Diminished call stretch as a result of renal hypoperfusion
        - Stimulation of beta-adrenergic nerves
        - Agents that increase adenylate cyclase acticity: adrenergic agonists, PGE2, PGI2, dopamine, histamine and parathyroid hormone
- **Angiotension II receptor subtypes**:
    - **AI1 receptor**- located at glomeruli and tubulointerstitium
    - **AII receptor**- located at cortical blood vessels
- **Activation of renal RAAS**
    - RAAS is activated by loss of blood volume or drop in blood pressure (e.g. hemorrhage). This loss of pressure is sensed by baroreceptors in the carotid sinus. However, in kidney this leads to decrease in GFR and filtered NaCl. This stimulates macula densa to signal juxtaglomerular (JG) cells of JG apparatus located in the afferent arterioles to release renin.
    - Renin cleaves angiotensinogen into angiotensin I (rate-limiting step)
    - Angiotensin I is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE), which is found mainly in lung capillaries.
    - AII is the most important product of RAAS, which is a powerful vasoconstrictor. Hypovolemia or hypotension is the most important physiologic stimulus for AII secretion. AII causes:
        - Release of aldosterone from the zona glomerulosa in the adrenal cortex, and thus stimulates sodium reabsorption
        - Increases peripheral vascular resistance to raise BP
- **Clinical significance of RAAS** lies in inappropriate activation of RAAS which occurs in cases of
    - Pperceived hypovolemia, such as renal artery stenosis, CHF, or advanced liver disease and leads to hypertension, inappropriate salt and fluid retention, or both.
    - Renin secreting tumors
    - ACE inhibitors are used as antihypertensives. These act by reducing formation of the more potent AII
    - AII receptor blockers (ARBs) can be used to prevent angiotensin II from acting on AII receptors, and thus are used in the treatment of HTN
    - Direct rennin inhibitors (e.g. Aliskiren) can also be used for HTN

6. Hyperfiltration injury

- **Definition:** Glomerular hyperfiltration injury has been variably defined as either:
    - Absolute increase in whole-kidney GFR, or
    - Increased filtration fraction, or
    - Increased filtration per nephron (SNGFR)
- It is important to realize that even with the loss of over 90% of renal function, most kidneys can continue to perform excretory and secretory functions at a level compatible with life because of compensatory physiologic and morphologic alterations.
- Cellular hyperplasia accounts for 10-25% of the increase in kidney size, while hypertrophy responsible for the rest. Increase in GFR is predominantly due to glomerular hypertrophy of remnant nephrons.
- **Etiopathogenesis:**
    - Physiological causes of increased GFR include: After high-protein meal, during pregnancy. Capacity to increase GFR after protein loading is termed renal functional reserve, and loss of this reserve is characteristic of CKD.
    - Increased GFR as an early manifestation of chronic diseases, e.g. DM
    - Increased SNGFR occurs as an adaptive response to nephron loss, and leads to glomerular hypertension and subsequent glomerulosclerosis with progressive renal function decline
    - Mechanisms of glomerular hyperfiltration injury in disease conditions are variable and not fully clear, although RAAS has been implicated as a contributing pathway
    - In cases of reduction in renal mass, the remaining nephrons undergo hypertrophy. There is associated reduced afferent arteriolar resistance and increased glomerular blood flow which leads to intraglomerular

hypertension. **This causes increased arterial stiffness (glomerular sclerosis) and tubule-endothelial dysfunction (proteinuria) leading to progressive kidney damage.**

  - Local activation of coagulation cascade and nitric oxide has also been implicated in pathogenesis

- **Mechanism**

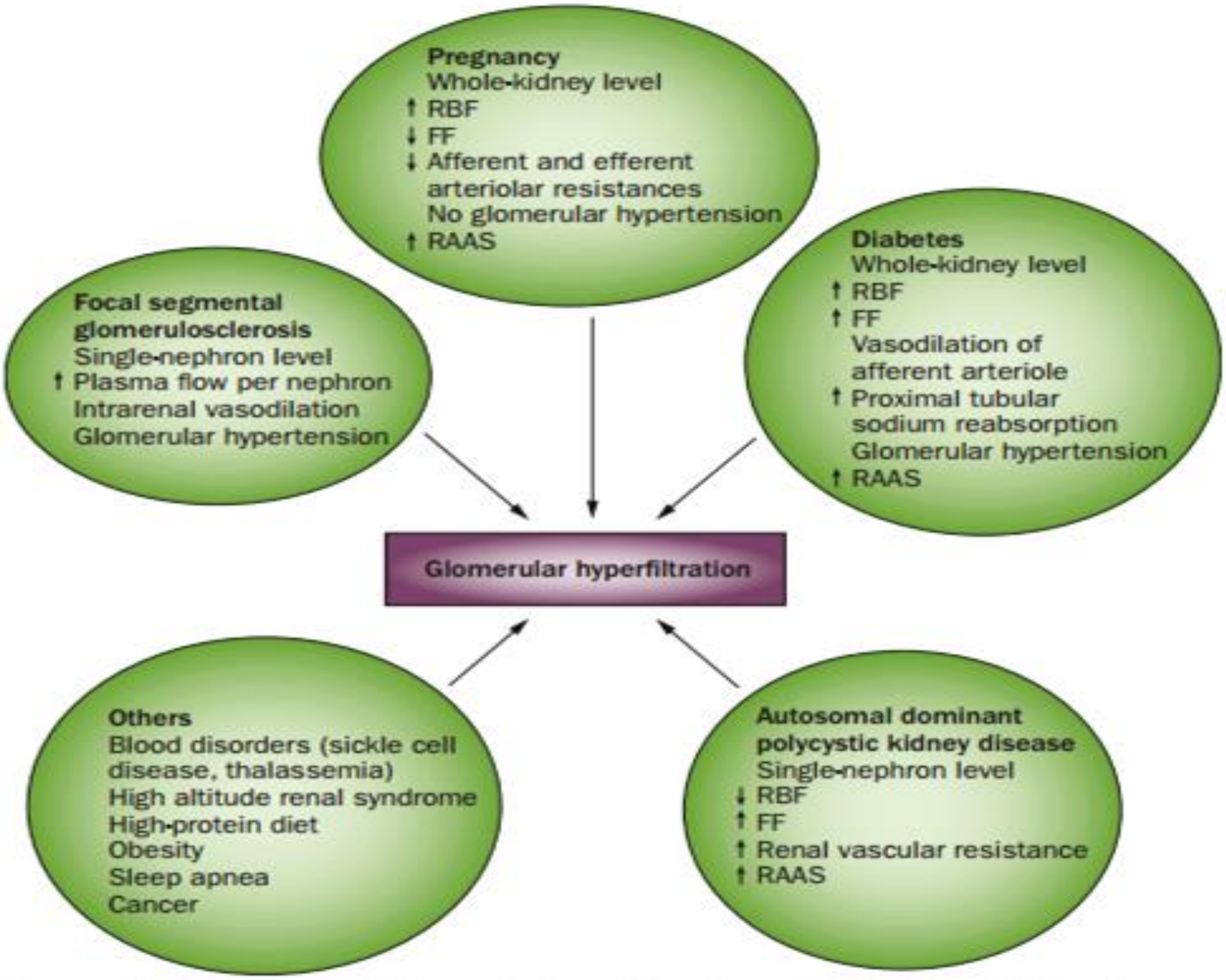
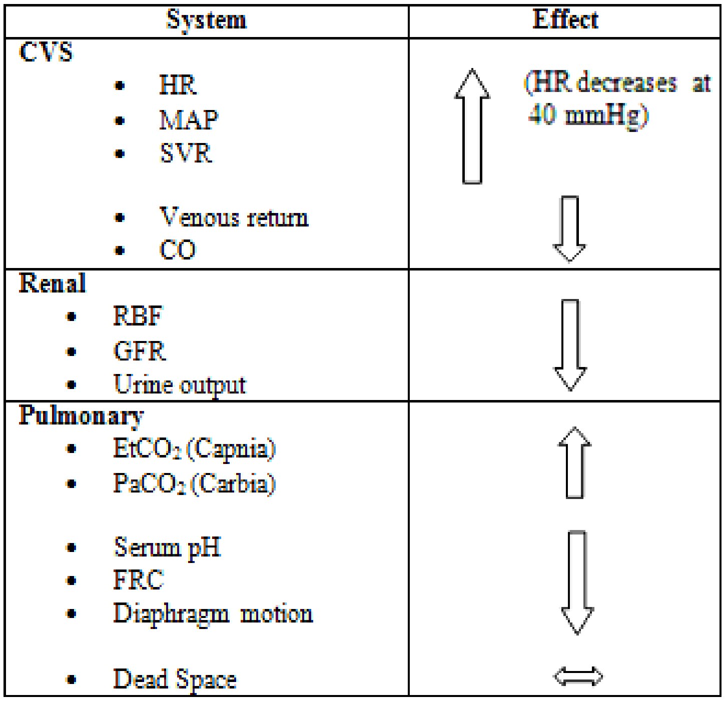

Pregnancy
Whole-kidney level
↑ RBF
↓ FF
↓ Afferent and efferent arteriolar resistances
No glomerular hypertension
↑ RAAS
Focal segmental glomerulosclerosis
Single-nephron level
↑ Plasma flow per nephron
Intrarenal vasodilation
Glomerular hypertension
Diabetes
Whole-kidney level
↑ RBF
↑ FF
Vasodilation of afferent arteriole
↑ Proximal tubular sodium reabsorption
Glomerular hypertension
↑ RAAS
Glomerular hyperfiltration
Others
Blood disorders (sickle cell disease, thalassemia)
High altitude renal syndrome
High-protein diet
Obesity
Sleep apnea
Cancer
Autosomal dominant polycystic kidney disease
Single-nephron level
↓ RBF
↑ FF
↑ Renal vascular resistance
↑ RAAS

Figure 1 | Mechanisms of glomerular hyperfiltration. Abbreviations: FF, filtration fraction; RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow.

- **Treatment of glomerular hyperfiltration renal injury**
  - Most effective intervention may be by targeting glomerular hypertension and RAAS.
  - Increase in glomerular pressure could be attenuated by blocking the vasoconstrictive effect of AII on the glomerular efferent arteriole.
  - ACEIs or ARBs promote regression of glomerulosclerosis
  - ACEIs and ARBs can retard progression of diabetic nephropathy
  - Proinsulin C-peptide, a potential renoprotective agent constricts glomerular afferent arterioles in diabetics thereby prevents glomerular hyperfiltration
  - Rosiglitazone is an insulin-sensitizing drug improves endothelial dysfunction, reduces glomerular hyperfiltration in early DM-2 and decreases ESRD and microalbuminuria
  - Avoidance of obesity, or weight loss, particularly in patients after unilateral nephrectomy (e.g. kidney donation) or those with underlying kidney disease, delays progression to ESRD.

7. Acid base changes in pneumoperitoneum

- **Physiologic effects of pneumoperitoneum with CO_2**



System	Effect
CVS • HR • MAP • SVR	⇧ (HR decreases at 40 mmHg)
• Venous return • CO	⇩
Renal • RBF • GFR • Urine output	⇩
Pulmonary • $EtCO_2$ (Capnia) • $PaCO_2$ (Carbia)	⇧
• Serum pH • FRC • Diaphragm motion	⇩
• Dead Space	⇔

* HR (Heart rate), MAP (Mean arterial pressure), SVR (Systemic vascular resistance), CO (Cardiac Output), RBF (Renal blood flow), GFR (Glomerular filtration rate), FRC (Functional residual lung capacity)

  - Lower the pneumo-pressure lesser is the post operative pain
  - **Hypercarbia** causes stimulation of sympathetic nervous system causing increase in HR, & ventricular extrasystole
  - But, **peritoneal irritation** causes vagal stimulation & bradyarrhythmias
  - With increasing intra-abdominal pressure CVP readings are unreliable (artificially raised) due to increased in intra-thoracic pressure. For accurate monitoring Swan-Ganz catheter is needed.
  - In **Trendelenburg position** (head down)→ CO, MAP- Increase, HR, SVR & vital lung capacity- Decrease
  - **Oliguria** is due to decrease in RBF & direct parenchymal compression
    - **Cortical RBF** decreases throughout from 5-40 mmHg of pneumo-pressure
    - **Medullary RBF** first increases up to 20 mmHg of pneumo- pressure & then decreases thereafter
  - Prevention of oliguria→
    - Keep pneumo- pressure 10 mmHg or less
    - Use I/V Lasix (20 times plasma creatinine in mg)
    - I/V Mannitol 12.5-25 mg
    - I/V Dopamine at the rate of 2 mcg/kg/min
  - **Acid-base alterations**
    - Underlying cause of respiratory acidosis is transperitoneal absorption of CO_2
    - Hypercarbia can develop in transperitoneal & retro-/extra-peritoneal laparoscopy, and it results in systemic acidosis with attendant fall in serum pH.
    - Acidosis is compensated by hypercapnia and respiratory compensation.
    - $EtCO_2$ is measured by 'Capnometer'
    - Intermittent ABG analysis is indicated during laparoscopy for all procedure of > 1h duration and in COPD patients. In later, ABG monitoring should extend into post-extubation recovery period.
  - Mesenteric & intra-abdominal visceral blood flow **decreases** during laparoscopy
  - **Adrenals**→ only intra-abdominal organ whose blood supply **increases** during laparoscopy
  - Incidence of GE-reflux & regurgitation→ does NOT increase
  - Theses hormone levels increase during laparoscopy→ Epinephrine, nor-epinephrine, dopamine, cortisol, beta-endorphins, prolactin, vasopressin (AVP)
  - Laparoscopy causes lesser degree of catabolic response than does open surgery
  - Immuno-suppression
    - Laparoscopy causes lesser degree of immuno-suppression than does open surgery. This may be translated to:
      - More favourable immunologic state (CO_2 is better than air in this regard)
      - Faster convalescence in laparoscopic surgeries
      - Lesser tumor-cell growth after laparoscopic than after open surgeries

8. Robotic surgery in Urology

- **Robotic system**
  - First commercially available robotic system→ RoboDoc
  - First commercial robotic system specifically for laparoscopic applications→ Automated Endoscopic System for Optimal Positioning (AESOP). This was the first robot to receive FDA approval.
  - Currently ONLY robotic system in wide spread use→ DaVinci Robotic System [Intuitive Surgical Sunnyvale, CA]. It has 3 main components:
    1. Robotic tower→ to which instruments are attached
    2. Surgeons console→ workstation on which surgeon sits & manipulates instruments
    3. Ancillary vision cart→ supports monitor, & also includes insufflators, light source & camera
- **Ports**
  - Camera port→ 12 mm
  - Other secondary ports→ 8 mm
  - All ports should be 8-10 cm apart
  - In transperitoneoscopy in flank position, lowest port should not be below umbilical level
  - Assistant port is place caudal or inferior to robotic ports
- **Advantages**
  - Hand-eye coordination in davinci, the display systemprojects the image in the direction of the surgeon's hands via a mirror overlay optical systemrestoring hand eye coordination. Zeus system has a high definition monitor at the eye level in front of the surgeon.
  - Depth perception
  - Intuitive movements
  - Precision
  - Ergonomic design
  - Telesurgery
- **Disadvantages**
  - Cost
  - Availability
  - Loss of tactile or haptic sensation
- **Urological Applications**

  Robotics have been most extensive used in urology for prostatic surgery
  - **Radical Prostatectomy**
    - One of the largest experiences with robot assisted radical prostatectomy (RARP) was at the Vattikuti Urology Institute with the daVinci system. RARP is clearly emerging as the front runner in new technologies in urology. Oncological, urinary and sexual outcomes are comparable to open approach
    - RARP achieves better and early/faster continence compared with open RP.
  - **Renal Surgery**
    - Most renal procedures such as a nephrectomy are standardized laparoscopic procedures require no reconstruction.
    - Most use of robot is for difficult ablative renal surgeries and reconstructive renal surgeries. These include radical nephrectomy, radical nephroureterectomy, partial nephrectomy, peyloplasty, ureterocalicolostomy etc.
    - Robotic technology is ideally suited to decrease the technical difficulty in this reconstructive procedure especially during intacorporeal suturing in pyeloplasty, ureterocalicolostomy and ileal ureter replacements. Reports also show shorter operative and anastomotic times with the robot when compared with pure laparoscopy.
  - **Adrenalectomy**
    - First human adrenalectomy using the robot in 2001. There have been a number of subsequent reports on the use of robot assistance for adrenalectomy.
    - While there was a higher operative time for robotic surgery, it progressively decreased with increasing experience.
  - **Cystectomy And Urinary Diversion**
    - Construction of the neobladder after radical cystectomy requires significant surgical skills and the robot is very helpful for this step.
    - With the possibility of fertility preserving cystectomy with ONB in females, robotic radical cystectomy may well become the standard of care for this debilitating condition.

- **Inguinal lymphadenectomy**
    - Robotic inguinal lymphadenectomy has recently been reported as robot is being combined to VEIL. It has been shown to provide all the advantages of minimal invasiveness with comparable oncological results.
    -
- **Others**
    - Robotic-Assisted Laparoscopic Sacrocolpopexy
    - Robots are being used to help enhance surgical skills especially in laparoscopy naïve surgeon.

9. Creatinine clearance

- GFR is the best reflection of total/global renal function. But GFR cannot be measured directly. GFR can be estimated by **measuring the rate of clearance of particular substances from the plasma.**
- Although, inulin clearance is the best or ideal for estimation of GFR, it is not clinically useful because it is difficult to administer (requires an intravenous infusion of inulin), and difficult to measure.
- **The most widely and practical method used to estimate GFR (eGFR) is 24-hour creatinine clearance (CrCl).**
- CrCl is calculated by determining creatinine concentration in timed urine collections and simultaneously in blood using the following equation
    - CrCl (mL/min) = [Urinary Cr (mg/dL) / Serum Cr (mg/dL)] x Urine volume (mL/min
- **Advantages of using CrCl**
    - **Cr is produced** endogenously, thus does not require outside administration
    - Produced at a constant rate in the body
    - Rate of production varies from individual to individual, but for a single individual daily variability is less than 10%.
    - Easy to perform, relatively cheaper, and readily available method
- **Disadvantages**
    - Less accurate than inulin clearance
    - Some creatinine is cleared from plasma through proximal tubular **secretion**
    - Thus CrCl overestimates the true GFR, on an average by 10% to 20%
    - Overestimation of GFR becomes even more important as GFR declines (CKD patients), because in CKD patients tubular secretion increases in response to increasing serum creatinine levels and may contribute up to 35% of all creatinine removal from the body at GFR levels of 40 to 80 mL/min.
    - Creatinine production which may be reduced as a result of factors such as malnutrition, advanced age or liver disease
    - Requires a timed urine collection, which has proven to be laborious, inconvenient and prone to collection failure, especially in the elderly and children
- **At best, then, the CrCl should be considered the "upper limit" of the true GFR.**
- **A number of mathematical formulas have been developed to improve the accuracy of CrCl.** Two most widely used are the Cockcroft-Gault and "modifcation of diet in renal disease" (MDRD) formulas.
    - **Cockcroft-Gault formula:** developed from data collected from individuals with normal renal function; it is a simple formula to estimate CrCl (not GFR) based on 3 variables: age, sex, and body mass. It has the advantage of being very simple, but is not as accurate as other methods in CKD patients.

$$\text{CrCl} = \frac{\{(140 - \text{age}) \times (\text{IBW in kg})}{[\text{PCr (mg/dL)} \times 72]\}} \times 0.85 \text{ (women)}$$

- **MDRD formula:** derived from data collected in patients with renal impairment. This is a more complex but more accurate than the Cockcroft-Gault. It estimates GFR, and is based on 4 variables: PCr, age, sex, and ethnicity). It does not require body weight and height, and is normalized to 1.73 m^2 body surface area.

$$\text{GFR (mL/min/1.73 m}^2) = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

- GFR estimate should be obtained in all patients with renal impairment (rather than a PCr alone), and the recommended method is through the use of the four-variable MDRD formula or Cockcroft-Gault formula.

10. Management of urological conditions in pregnancy

- **Physiologic changes**
    - Renal length increases-1 cm.
    - The collecting system-decreased peristalsis.
    - Hydroureter-due to the muscle-relaxing effects of increased progesterone and to mechanical obstruction of the ureters.
    - Uterus displaces the bladder-superiorly and anteriorly.
    - GFR increases-30% to 50%.
    - Serum creatinine levels >0.8 mg/dL- further evaluation of renal function is required.
    - Urinary protein is not considered abnormal until >300 mg of protein in 24 hours is excreted.
    - Increased renal plasma flow and GFR lead to a decrease in the resistance index (RI)
- **Urological conditions in pregnancy and their management**
    1. LUTS
        - Frequency, nocturia, and urgency in the absence of UTIs are common in pregnancy, and increase as the pregnancy progresses.
        - Frequency appears in 76- 95% of pregnant women, nocturia in 56-72%, and urgency in 63-68%.
        - Causes are increased GFR and diuresis, longer periods of time in supine position, increased fluid intake, and the mechanical pressure of the uterus in the pelvis, which reduces bladder capacity.
        - Treatment: involves limiting inappropriately high fluid intake, position changes etc.
    2. Urinary retention during pregnancy
        - Incidence of AUR in pregnancy is 1/3000-1/8000 pregnancies, and usually occurs between the 12th-14th weeks when uterus is retroverted.
        - Causes include- Narrow pelvis, Myoma, Uterine abnormalities, action of high doses of progesterone (smooth muscle relaxation, detrusor inactivity)
        - Treatment: AUR is usually temporary and catheterization and bimanual manipulation of the uterus to an anteverse position is usually sufficient. This retention usually resolves by 16 weeks' gestation as the uterus grows out of the pelvis.
    3. Urinary incontinence
        - Incidence: UI is common pregnancy with stress incontinence (SUI) being more prevalent (40%) than urge incontinence (5-20%). Incidence increases as the pregnancy progresses.
        - It is associated with age, parity and BMI.
        - Treatment: Most common advice is pelvic floor exercises and bladder retraining. Patient should be reassured as UI usually subside in majority.
    4. Urinary tract infections
        - Prevalence of asymptomatic bacteriuria in pregnant women- 4% to 7%.
        - Prevalence of pyelonephritis in pregnant women- 1% to 4%.
        - Incidence of cystitis is twice that of pyelonephritis.
        - Prevalence of pyelonephritis in pregnant women with bacteriuria- 20% to 40%. Thus, screening and treatment of asymptomatic bacteriuria is recommended in all pregnant women.
        - Risk factors: older multiparous women, sexual activity, history of previous UTIs, and VUR. Factors related to pregnancy include enlarged, hyperemic kidneys with increased GFR, dilated ureters due to uterine pressure and smooth muscle relaxation, inadequate emptying of the bladder due to anterior displacement of bladder by enlarged uterus, pregnancy-related immunosuppression.
        - Common causative organisms: Escherichia coli are the most common infecting organisms, responsible for 75-90% of bacteriuria during pregnancy; but Klebsiella, Proteus and Pseudomonas are not uncommon.
        - Diagnosis:
            - In a pregnant woman with symptoms→ Positive urine culture (>10^3 cfu/mL organisms) with pyuria.
            - In cases of asymptomatic bacteriuria→ values >105 cfu/mL in two cultures 24 h apart are considered significant.
        - Treatment:

        - Cystitis and asymptomatic bacteriuria: short courses of antibiotics lasting 3-5 days. Recommended drugs include Nitrofurantoin (contraindicated in labor at term), penicillin (Amoxi-clavulanate), cephalosporins. Cotrimoxazole (should be avoided in the1st and 2nd trimesters)
        - Pyelonephritis: longer courses of 7-10 days (with i/v administration for first 24-48 hours. Recommended drugs include penicillin, cephalosporins, and monobactams.
        - Recurrent infections: AMA prophylaxis until delivery should be considered (nocturnal or postcoital suppressive therapy). Recommended drugs include Cephalexin, and Nitrofurantoin.

5. Hydronephrosis and HUN
    - Mild HUN is considered a normal phenomenon and may be present in up to 90% of pregnancies.
    - Increased diuresis, small stones or other unrecognized obstruction may cause decompensation of ureteral function, progressing to symptomatic acute hydronephrosis.
    - Untreated HDN has the risk of developing life-threatening infection, which may endanger the life of mother and the fetus.
    - Symptomatic HDN usually resolve with conservative treatment→ analgesia, intravenous (IV) fluid and IV antibiotics on signs of infection.
    - On failure of conservative measures (non-resolving signs of renal infection after 48 h, deteriorating renal function and worsening loin/flank pain), drainage with a double J ureteric stent or PCN is recommended.
6. Renal colic and stone disease during pregnancy
    - This is the most common cause of non-obstetric abdominal pain requiring hospitalisation.
    - Incidence: Despite the theoretically increased risk of urinary calculi in pregnancy (urinary stasis, obstruction and infection), the incidence is 0.03-0.5% and no different from the non-pregnant woman.
    - Urinary stones usually appearing in the 2nd or 3rd trimester (80-90%). Symptomatic stones are found in the ureter twice as often as in the renal pelvis and affect both ureters with equal frequency.
    - Calcium phosphate stones (70%) are more common than calcium oxalate (30%).
    - Symptoms: Low back pain (most common), hematuria (2nd most common symptom), frequency, UTI (especially with struvite stones).
    - Diagnosis: USG is the diagnostic method of choice. The use of ionizing radiation techniques must be evaluated on a case-by-case basis. MRI, although it produces no irradiation, does not correctly detect lithiasis.
    - Issues
        - Many signs and symptoms can be found in normal pregnancy.
        - Potential adverse effects of radiation, anaesthesia and surgery often complicate the diagnostic and treatment modalities.
        - Most stones (64-84%) pass spontaneously with conservative treatment. But those that do not pass may induce premature labour or cause urosepsis.
    - Treatment
        - First step is conservative treatment analgesic and fluid therapy.
        - If conservative management fails, ureteral stent insertion or a placement of percutaneous nephrostomy tube may be appropriate (with a high risk of encrustation due to hypercalciuria typical of pregnancy).
        - Ureteroscopy with stone manipulation for distal ureteral stone during pregnancy has been reported.
        - Definitive surgery should therefore be delayed until 6–8 weeks postpartum if possible.
        - ESWL is contraindicated in pregnancy because of the effect of the shockwave on the fetus potentially resulting in fetal death.
7. Urological malignancies
    - Incidence: urological tumors occur with an incidence of 1/1000 pregnancies.
    - Relatively common types of tumor
        - Bladder tumors: rare. Initial treatment includes TURBT. Treatment of low-risk tumors can be delayed.

- RCC
    - Incidence: the most frequently diagnosed urological tumor during pregnancy, accounts for half of all primary urological tumors in pregnancy.
    - Symptoms: pain, palpable mass, hematuria, and hypertension.
    - Diagnosis: ultrasound or MRI.
    - Treatment: radical nephrectomy, preferably via laparoscopy.
    - Important considerations
        - After 20th week laparoscopy becomes technically less feasible. 2nd trimester being safest for laparoscopy
        - Trocar placement should be more cephalad
        - Preferred site of entry- right & left Palmer points rather than umbilical or paraumbilical
        - Keep working pressure of 10 mmHg, as prolonged pressure of >15 mmHg can result in hypotension
        - Prolonged CO_2 pneumoperitoneum can cause- maternal hypercarbia & fetal acidosis
- Angiomyolipoma
    - Incidence: Most common benign tumor during pregnancy. Usually single and unilateral.
    - Usually asymptomatic. The onset of symptoms is associated with spontaneous rupture (pain, hematuria, and retroperitoneal mass).
    - Diagnosis: ultrasound or MRI.
    - Treatment: if tumor is asymptomatic, monitoring is recommended. If symptomatic with bleeding and hemodynamic instability, the best option is angiographic embolization.
- Pheochromocytoma
    - Incidence: Rare tumor (1/50,000 pregnancies).
    - Usually presents with severe or fluctuating HTN, headache, palpitations, hyperhidrosis, nausea, vomiting, changes in vision, or CHF
    - Diagnosis: Determination of catecholamines or their metabolites in 24 h urine. The diagnostic imaging test of choice is MRI (bright lesions on T2-weighted images).
    - Treatment of choice is surgical excision. After diagnosis, treatment with α-blockers should be started. About 1-2 weeks later β1 blockers (Atenolol) should be added.

Post obstructive diuresis

Refers to dramatic increase in urine output after the release of Urinary tract Obstruction.

Definition: Urine production exceeding 200 mL per hour for 2 consecutive hours or producing greater than 3 L of urine in 24 hours is diagnostic of POD

Factors necessary are

- Accumulation of total body water, Sodium and urea
- Impairment of Tubular re-absorptive capabilities. (in pathological POD)

Clinical scenarios with significant POD

>Prior bilateral ureteral obstruction (BUO)
> unilateral obstruction of a solitary functioning kidney
>Uncommon following UUO due to compensation by normally functioning contralateral kidney.

Types

- **Physiological Diuresis** - Self limiting, generally lasts 24 hours– As a response to simple solute and water overload. Stops after return to euvolemic state.
- **Pathological Diuresis - g**enerally lasts longer than 48 hours and can be exacerbated with excessive intravenous fluid replacement. Inappropriate diuresis of water beyond euvolemic state.

Contributing factors after the release of obstruction

- ➢ Physiological
  1. Excess Na and water retention
  2. Retention of urea and non reabsorbable solutes
  3. Accumulation of ANP
- ➢ Pathological
  1. Concentration defect
  2. Decreased tubular reabsorption of Na
  3. Insensitivity to ADH
  4. Increased tubular flow reducing equilibration time for reabsorption of Na and water

Derangement of Urinary concentrating ability

- Normal urine concentrating ability requires a hypertonic medullary interstitial gradient because of
  - active salt reabsorption from the thick ascending limb of Henle,
  - urea back flux from the inner medullary collecting duct, and
  - water permeability of the collecting duct mediated by vasopressin and aquaporin water channels.
- Obstructive nephropathy can disrupt some or all of these mechanisms and lead to deficits in urinary concentration

Insensitivity to ADH

Dysregulation of aquaporin water channels in the proximal tubule, thin descending loop, and collecting duct may contribute to the long-term polyuria and impaired concentrating capacity caused by obstructive nephropathy.

Defects in Sodium Transport

- Active transport of Na+ across cell membranes requires apical entry through selective Na+ transporters or channels and basolateral exit driven by sodium-potassium adenosine triphosphatase (Na+,K+-ATPase) and adequate adenosine triphosphate (ATP) must be generated to drive these primary transport steps.
- In obstruction there is reduced activity of the apical Na channel (ENaC) and also decreased ATPase activity.

Role of ANP

- increases afferent arteriolar dilation
- efferent arteriolar vasoconstriction, thus increasing glomerular capillary hydraulic pressure
- decreases the sensitivity of tubuloglomerular feedback
- inhibits release of renin,
- secreted ANP contributes to a profound diuresis and natriuresis.

MONITORING

- These individuals should have their urine output recorded every hour initially and vital signs checked every 6 to 8 hours.
- Further, their serum electrolyte (especially potassium), magnesium, phosphate, urea, and creatinine levels should be checked every 12 to 24 hours and corrected if necessary.
- The intensity of monitoring depends on presence of risk factors for postobstructive diuresis and the subject's mental status, renal function, and electrolyte status.
- A urine sample should be collected for urinary sodium and potassium levels and urine osmolality to determine if it is a salt or urea type of diuresis. Urea diuresis is generally self-limiting, whereas salt diuresis can convert to pathologic POD and requires careful monitoring of serum electrolyte levels and hydration status.
- Spot urine sodium levels greater than 40 mEq/L suggest renal tubular injury and if prolonged can lead to pathologic POD.
- *A simple method to estimate urine osmolality, if an automated method is not available, is to assess the urine specific gravity.* A specific gravity of 1.010 is iso-osmotic with serum osmolality, indicating that the kidneys do not need to concentrate the urine. This is consistent with physiologic POD and is generally self-limiting. A specific gravity of 1.020 demonstrates that the kidneys are concentrating the urine and POD has resolved or has nearly resolved. However, a specific gravity of 1.000 is hypo-osmotic with serum osmolality, indicating the kidneys' inability to concentrate the urine. This is consistent with pathologic salt-wasting POD and should alert the health care team to monitor the patient closely

TREATMENT

- In the first 24 hours, urine output should be checked hourly.
  - ➢ If it is over 200 mL/hour, then 80% (50% at CMCH) of the hourly output should be replaced intravenously with 0.45% saline. Alternatively the same volume of water may be consumed orally.
- After 24 hours of persistent diuresis,
  - ➢ total fluids infused should be about 1 L less (or <75%) than the previous day's output, provided the patient is hemodynamically stable.
- Once the urine output </- 3 L per day, oral fluids should suffice.
- If there are signs of hypovolemia, then total fluids replaced should be about 0.5 L less, instead of 1 L, than the last 24 hours' output.

Key Words: physiology, water-electrolyte imbalance, ureteral obstruction, urinary bladder neck obstruction, diuresis

INTRODUCTION

Obstruction to urine flow can occur anywhere along the urinary tract. The site, chronicity and degree (partial or complete) of obstruction, in conjunction with underlying health and comorbidities, will affect the resulting physiological changes and clinical presentation. More severe effects occur with prolonged obstruction and the complete impediment of urine flow, such as from bilateral ureteral obstruction. However, unilateral ureteral obstruction can also have long lasting consequences to the affected renal unit. There are many causes of obstructive uropathy, and various tools can be used to aid in the diagnosis. Once urine flow has been restored, subsequent physiological changes occur as the body attempts to restore homeostasis. Recovery from urinary obstruction can result in a period of significantly increased urine production with possible electrolyte and volume status derangements leading to serious consequences if not managed appropriately. Management of this post-obstructive diuresis is the focus of this Update.

DEFINITIONS

Several terms are used when describing urinary tract obstruction. Hydronephrosis is an anatomical term describing dilatation of the renal pelvis and/or calyces. Obstructive uropathy refers to the blockage of urine flow in the urinary tract. **It should be noted that hydronephrosis and obstructive uropathy are not interchangeable terms.** Hydronephrosis may occur in the presence or absence of obstruction and obstructive uropathy can occur without hydronephrosis. Obstructive nephropathy is the resulting renal dysfunction that may occur secondary to obstructive uropathy. **There is no consensus on the definition of polyuria. Commonly, polyuria is defined by volume-based definitions, often reporting urine flow >3 to 4 liters a day which is considered to be inappropriately high.**[1, 2] This definition is not applicable when the diuresis is appropriate for a given excess of water or solute.

Other definitions focus on physiological factors, such as an inappropriately high urine volume relative to the clinical situation. For example, while a patient with a daily post-obstructive urine volume >4 L would fulfill the numeric definition of polyuria, if the polyuria is appropriate for the clinical situation, the ‘‘inappropriately high’’ definition of polyuria would not be met. **Post-obstructive diuresis refers to the polyuria that may be encountered after relief of urinary obstruction as the body attempts to restore fluid and solute homeostasis.** POD may be physiological or pathological. Physiological POD is an appropriate diuresis in response to the volume and solute overload that is self-limiting and stops when homeostasis is restored. Pathological POD is an inappropriate diuresis in response to the volume and solute overload leading to derangements in blood chemistry and/or volume status. For example, a pathological water diuresis can cause hypernatremia and a pathological sodium loss can cause hypovolemia.

INCIDENCE

It is difficult to accurately determine the overall incidence of urinary tract obstruction given the numerous etiologies and presentations. In a large review from more than 60 years ago of 59,064 autopsies ranging from infants to octogenarians hydronephrosis was found in 3.3% of males and 2.9% of females (overall rate of 3.1%).[3] Hydronephrosis was more prevalent in women 20 to 60 years old and more common in men after age 60 years. It is difficult to determine how many of these cases were truly secondary to obstructive uropathy, and the relevance of this study in the modern era of medicine is not certain.

The majority of reports on obstructive uropathy focus on select populations. For example, the incidence of acute urinary retention in men ranges from 2.2 to 6.8/1000 person-years in the general population and increases to 18.3 to 25/1000 person-years in men with lower urinary tract symptoms from presumed benign prostatic hyperplasia.[4-6] Although the overall incidence of obstructive uropathy is difficult to accurately assess, it is nonetheless a commonly seen urological problem with potentially devastating consequences.

The reported incidence of POD after relief of obstruction is highly variable, ranging from 0.5% to 52% in cases of urinary retention.[7, 8] Some of this variation is due to differences in the definition of POD. Of 62 patients in the intensive care unit with acute kidney injury of post-renal etiology POD, defined as urine output >4 liters daily, developed in 63% after relief of the obstruction.[9] Urinary retention was the etiology of the obstruction in 52% of cases and 11% had BUO or UUO in a solitary kidney. POD is uncommon in cases of UUO with 2 functioning kidneys as the unobstructed kidney maintains solute and fluid balance.

There are numerous potential causes of urinary tract obstruction. Congenital and acquired etiologies can cause obstruction but we will focus on the latter in this Update**. The location of obstruction can be anywhere along the urinary tract from the renal pelvis distally to the urethral meatus. Possible etiologies are listed in the Appendix.**

RENAL PHYSIOLOGY OF URINARY OBSTRUCTION

The changes in renal physiology resulting from ureteral obstruction have been well studied in animal models. While there may be similar etiologies of obstruction, the renal responses to UUO versus BUO or obstruction of a solitary kidney are different. **In general, a healthy contralateral kidney can usually compensate for an obstructed kidney minimizing volume and solute derangements seen with BUO.**

Effect of obstruction on collecting system pressure, renal blood flow and glomerular filtration rate. The obstruction to urinary

ABBREVIATIONS: BUO (bilateral ureteral obstruction), CRF (chronic renal failure), CT (computerized tomography), GFR (glomerular filtration rate), IV (intravenous), IVP (excretory urography), MRI (magnetic resonance imaging), POD (post-obstructive diuresis), UUO (unilateral ureteral obstruction)

flow leads to an increase in ureteral pressure extending proximally to the kidney. This pressure is a direct result of the retained urine within and the compliance of the system. Secondary to this increased pressure, hydronephrosis can become apparent. The amount of pressure on the renal parenchyma can be decreased by pelvicalyceal rupture and subsequent urinary extravasation. Urine may also be absorbed through venous backflow (pyelovenous flow) or by the lymphatic system (pyelolymphatic flow).[10]

There are 3 time dependent phases to changes in collecting system pressure, renal blood flow and GFR in UUO which differ from BUO. The renal physiological alterations in urinary obstruction are summarized in figure 1. The first (early) phase of UUO occurs during the initial few hours of obstruction and is characterized by an increase in pressure in the collecting system. However, GFR is maintained or slightly decreased due to an increase in renal blood flow from afferent arteriolar vasodilation.[11] Several mechanisms for this increase in renal blood flow have been postulated, including vasodilation from prostaglandins, nitric oxide and tubuloglomerular feedback.[12-16] Administration of either a prostaglandin synthesis inhibitor or a nitric oxide synthase inhibitor has been shown to block the vasodilatory response.[12, 17]

The second (mid) phase occurs immediately after the first phase and lasts several hours. It is characterized by a persistent elevation in pressure within the collecting system but a decline in renal blood flow and GFR.[18, 19] The decline in GFR occurs from an increase in efferent arteriole resistance. Activation of the renin-angiotensin system appears to play a role in the efferent arteriole vasoconstriction along with endothelin and thromboxane A_2.[20-23] During phase 3 of UUO renal blood flow continues to decrease. However, there is now an associated decrease in the collecting system pressure. By about 24 hours after obstruction, the pressure has declined to pre-occlusion levels or even less.[24] GFR remains decreased compared to baseline.

In cases of BUO complete obstruction of urinary flow results in anuria. Similar to UUO, there is an initial increase in renal blood flow with BUO but this response appears to be less pronounced and of shorter duration. A large decrease in renal blood flow follows.[25] The collecting system pressure remains elevated for longer and is often still high in animal models at 24 hours.[19, 26] It is believed that this persistent increased pressure is secondary to afferent arteriolar vasodilation and efferent arteriolar vasoconstriction, which may be caused by the accumulation of atrial natriuretic peptide or other factors associated with complete obstruction.[24, 27]

The recovery of GFR is difficult to predict but is significantly impacted by the duration of the obstruction and preobstruction renal function. Most studies examining this temporal relationship are in animals. After 24 hours of unilateral ureteral obstruction GFR returned to baseline within 2 weeks in a rodent model.[28] In dogs return of GFR was complete after 7 days of obstruction but it progressively decreased with longer periods (up to 6 weeks) of obstruction.[29] In a retrospective study of patients without preexisting chronic renal failure treated for acute renal injury attributed to obstructive causes, CRF developed at 3 months in 21% and 6% had end stage renal disease.[9] Predictors of CRF on admission were lower blood hemoglobin, lower serum bicarbonate and time lapsed until release of the obstruction. After release of obstruction, a lower initial diuresis during the first 24 hours (<4 L), absence of POD and higher

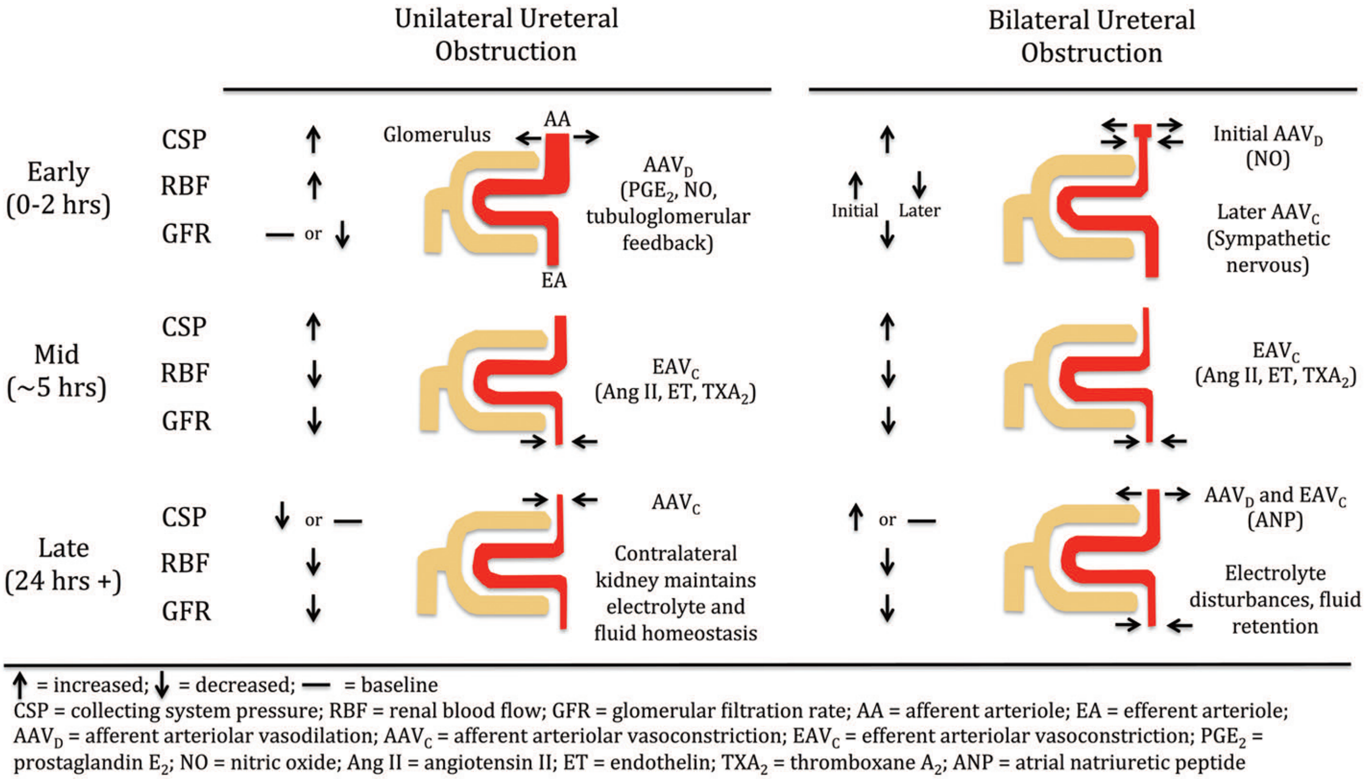

Unilateral Ureteral Obstruction
Bilateral Ureteral Obstruction
Early (0-2 hrs)
CSP
RBF
GFR
or
Glomerulus
AA
EA
AAV_D (PGE_2, NO, tubuloglomerular feedback)
Initial
Later
Initial AAV_D (NO)
Later AAV_C (Sympathetic nervous)
Mid (~5 hrs)
CSP
RBF
GFR
EAV_C (Ang II, ET, TXA_2)
EAV_C (Ang II, ET, TXA_2)
Late (24 hrs +)
CSP
RBF
GFR
or
AAV_C
Contralateral kidney maintains electrolyte and fluid homeostasis
or
AAV_D and EAV_C (ANP)
Electrolyte disturbances, fluid retention
↑ = increased; ↓ = decreased; — = baseline
CSP = collecting system pressure; RBF = renal blood flow; GFR = glomerular filtration rate; AA = afferent arteriole; EA = efferent arteriole; AAV_D = afferent arteriolar vasodilation; AAV_C = afferent arteriolar vasoconstriction; EAV_C = efferent arteriolar vasoconstriction; PGE_2 = prostaglandin E_2; NO = nitric oxide; Ang II = angiotensin II; ET = endothelin; TXA_2 = thromboxane A_2; ANP = atrial natriuretic peptide

Figure 1. Renal physiological alterations in urinary obstruction

urinary sodium were also associated with development of CRF in univariate analysis.

Alterations in concentrating ability, electrolyte homeostasis and acid/base balance. **The changes in urinary system pressure, renal blood flow and GFR impact the ability of the nephron to function properly, and maintain fluid and electrolyte homeostasis.** The ability of the kidneys to concentrate urine is impaired by obstruction. There appears to be a disruption of the medullary hypertonic interstitial gradient, leading to a loss of the osmotic driving force for water to move into the interstitium.[30] Studies in rats have also shown that bilateral ureteral obstruction leads to a decrease in the expression of aquaporins that are important in the absorption of water.[31, 32]

Renal handling of sodium is also altered with obstruction. There is an overall decrease in the transport of sodium in the nephron that can contribute further to the decreased concentrating ability of the kidney. Studies have demonstrated less activity and a fewer number of sodium transporters within the nephron in cases of obstruction.[33-35] BUO also prevents excretion of potassium, phosphate and magnesium. In cases of UUO the overall balance of these electrolytes is maintained by compensation from the contralateral kidney. Obstruction also leads to impaired urinary acidification, which appears to be from impaired H^+ excretion and bicarbonate transport within the tubule.[36]

Other renal effects of obstruction. Urinary obstruction leads to apoptosis of tubular and interstitial cells. In rats tubular cells were observed to undergo apoptosis after about 4 days of obstruction and interstitial cell death continued throughout the period of obstruction.[37] Inflammation and fibrosis of the intersitium can also occur from obstructive uropathy. This process appears to involve multiple factors including angiotensin II, tumor necrosis factor-α, transforming growth factor-β and nuclear factor-κB.[10]

SIGNS, SYMPTOMS AND PRESENTATION

Urinary tract obstruction is widely variable in presentation, ranging from asymptomatic to critically ill. The symptoms vary depending on the rate of onset, mechanism and degree of obstruction. Patients with bilateral ureteral obstruction or obstruction in the lower urinary tract may present with anuria which may be associated with signs of volume overload, electrolyte abnormalities and eventually CRF. There may or may not be pain, depending on the acuity of the obstruction. Suprapubic pain is often associated with urinary retention. Renal colic may be noted with an obstructing ureteral stone secondary to increased pressure and stretching in the wall of the collecting system and renal capsule. Certain etiologies may lead to hematuria. Weight loss or early satiety may occur and is more worrisome for a malignant etiology. Fever or leukocytosis may point towards an infectious cause. A history of lower urinary tract symptoms may indicate a prostatic cause.

It is important to elicit a good history including present illness assessing the acuity and type of symptoms. Symptoms of CRF (eg drowsiness, anorexia, fatigue etc) should be elicited. The medical history should be reviewed to assess for any prior genitourinary or renal conditions or diseases with potential urinary tract sequelae. Any prior abdominal, retroperitoneal or pelvic surgeries should be noted. Family and social histories should also be obtained. It is important to note any medications the patient is taking, as drugs such as protease inhibitors can cause stones and anticholinergics can lead to urinary retention.

Physical examination should start by obtaining vital signs to look for indications of infection (eg fever, tachycardia, hypotension) or volume overload (hypertension). Abdominal examination should make note of any pain or palpable masses (or distended bladder). The flank should be examined for costovertebral angle tenderness, ecchymosis or a palpable mass. A thorough genital exam should be performed along with a rectal exam and in women a pelvic exam when indicated. The volume status of the patient should be noted along with any signs of CRF (eg edema, pericardial rub, asterixis).

IMAGING

Given the varying presentations and etiologies of obstructive uropathy, imaging remains an important diagnostic tool. Potential studies include IVP, ultrasound, CT, MRI, nuclear renography and retrograde/antegrade ureteropyelography.

IVP. This study may be suggestive of urinary tract obstruction through a delayed nephrogram or pyelogram. Further delayed images may show a point of possible obstruction in the upper urinary tract. IVP involves intravenous contrast and radiation which limit its applicability to those with renal insufficiency or pregnant patients. While long considered to be the gold standard test for imaging of the collecting system and ureters, IVP has largely been supplanted by other imaging modalities.

Ultrasound. Ultrasound remains one of the most important imaging modalities for assessment of possible obstructive uropathy. It does not involve the use of contrast or radiation and is comparatively less expensive than other imaging modalities. It is one of the best studies for imaging hydronephrosis but it provides limited visualization of the ureter. However, the finding of hydronephrosis is suggestive but not diagnostic of urinary tract obstruction. Additional components can be added to the study to provide further evidence of a possible obstruction, such as measuring the resistive index or examining for a ureteral jet. An elevated resistive index may be suggestive of an obstruction.[10] Compared to a non-obstructed ureter, the obstructed ureter may not demonstrate a jet or may have a jet of less frequency, shorter duration and lower peak velocity on color Doppler.[38, 39]

CT. Non-contrast and contrast enhanced scans are powerful and commonly used imaging modalities for assessment of obstructive uropathy. CT provides improved anatomical details of much of the urinary tract not seen with IVP or ultrasound. It can also be performed relatively rapidly but involves radiation exposure. Non-contrast CT excels at diagnosing nephrolithiasis. However, protease inhibitor calculi are not visualized.[40] Contrast enhanced CT allows for further assessment of the urinary tract through nephrogenic and excretory phase imaging. Caution must once again be used in those with renal insufficiency and contrast allergies.

MRI. MRI offers the benefit of cross-sectional imaging without the use of radiation and is useful for the assessment of obstructive uropathy. MRI is generally more expensive than CT but is useful in pregnancy. Gadolinium contrast agents should be used with caution in patients with more severe renal disease (eg end stage renal disease on dialysis or estimated GFR <30 ml/minute/1.73 m^2 not on dialysis) given the potential risk of nephrogenic systemic fibrosis.[41]

Nuclear renography. Nuclear renography provides an assessment of potential urinary tract obstruction with functional data as well. The test involves the use of an intravenously administered radiopharmaceutical agent. The renal uptake and clearance of the administered agent allow for calculation of renal function and assessment of obstruction. **Traditionally, if 50% of the agent is not cleared within 20 minutes, the renal unit is considered obstructed.**[10] Consideration should be given to performing the test with a urinary catheter in place to avoid confounding factors such as urinary retention or vesicoureteral reflux. Delay in uptake and clearance of the agent can also be affected by renal insufficiency. The study can be modified by intravenous hydration and the addition of a diuretic to improve diuresis and help with assessment of obstruction. Nuclear renography provides the least overall anatomical definition compared to other modalities.

Retrograde/antegrade ureteropyelography. These techniques allow for anatomical assessment of the collecting system and ureter. The antegrade approach requires percutaneous access to the renal collecting system while the retrograde approach necessitates cystoscopy for ureteral cannulation. They can be considered for certain patients with intravenous contrast allergies but ionizing radiation is used.

OTHER DIAGNOSTIC TESTS

Serum electrolytes, blood urea nitrogen and creatinine should be checked at presentation. White blood cell count should be measured if there is concern for infection and hemoglobin/hematocrit should be checked to assess for anemia. Urinalysis should also be performed if possible, as crystals may indicate nephrolithiasis. Microhematuria may be indicative of a stone as well but is also worrisome for a malignant process. Bacteriuria or pyuria suggests an infectious process. A baseline urine osmolality should be obtained as it may help determine if subsequent diuresis is mainly water, solute or mixed. A patient should also be assessed for urinary retention. A full bladder can be seen on imaging or can be palpated on exam, and a bladder scan can be used to quickly assess bladder volume and suggest urinary retention at the bedside.

The Whitaker test allows for direct measurement of renal pelvic pressure during the fixed rate filling of a fluid.[42] The test is invasive and requires percutaneous access to the renal pelvis and placement of a urinary catheter. Traditionally, subtraction of the bladder pressure from the renal pelvic pressure would indicate obstruction if this value was >22 cm H_2O, normal if <15 cm H_2O and equivocal if between those values. However, studies have questioned the reliability of this test.[43, 44] Given the invasive nature and unclear applicability of the results, its clinical use is limited.

MANAGEMENT OF POST-OBSTRUCTIVE DIURESIS

The management of obstructive uropathy varies depending on the etiology and clinical status of the patient but intervention to relieve the obstruction should be considered. With obstruction below the level of the bladder, a urethral catheter should be placed. If this cannot be done, a suprapubic catheter should be considered. Ureteral obstruction can be relieved by either retrograde or antegrade placement of ureteral stents or a percutaneous nephrostomy tube. The urgency of these interventions depends on the symptoms, degree of obstruction, renal function, signs of infection and risks of the procedure. Since the long-term negative effects on renal function are increased the longer an obstruction persists, intervening as quickly as possible can preserve renal function, especially since the duration of the obstruction is often not known. Options for definitive relief of the obstruction can then be considered depending on the etiology once the patient has stabilized.

In the past some recommended intermittent or gradual drainage of an obstructed bladder, which was thought to potentially decrease the rates of hematuria and hypotension. However, with quick drainage the rates of hematuria are generally low (2% to 16%) and not severe, while the decrease in blood pressure represents a normalization of the pressure without cardiovascular compromise.[45] **As a result, intermittent or gradual drainage is no longer recommended.**

Once the obstruction has been relieved, some patients are at risk for potentially life threatening polyuria and electrolyte abnormalities as the kidney attempts to restore solute and fluid homeostasis. **Post-obstructive diuresis is usually a temporary phenomenon, and management is focused on avoiding volume depletion and electrolyte imbalances. Patients with complete urine impediment, such as obstruction below the level of bladder, BUO and UUO of a solitary kidney, are at higher risk.** Urine output can be robust during this phase of diuresis. While physiological diuresis occurs with the relief of obstruction, further diuresis can also be iatrogenically induced during management, such as when unnecessary or inappropriate fluids are given. Pathological diuresis can also develop characterized by the deranged renal regulation of the excess fluid and solutes.

Physiological diuresis. The majority of patients will experience physiological diuresis after relief of obstruction. This process resolves once the kidneys have been able to remove the excess water and solute accumulated during the obstruction. Vital signs, volume status, serum electrolytes, blood urea nitrogen and creatinine should be noted at presentation. **Once urinary drainage has been obtained, urine output should be closely monitored and a baseline urine osmolality obtained. The osmolality of the urine can indicate if the diuresis is more of a water or solute/osmotic diuresis.** During the obstruction, water retention can lead to expansion of the extracellular volume that leads to water diuresis as the extracellular volume is restored.

Water diuresis is defined by a lower urine osmolality (often <150 mOsm/kg).[1] Urea and other solutes can also be accumulated during obstruction leading to a solute/osmotic diuresis as they are increased in the glomerular filtrate after urine flow is restored. The increase in GFR with relief of obstruction leads to more of this filtrate being delivered to the tubules. Increased GFR can combine with an impaired ability to concentrate the urine, secondary to the effects of obstruction, and result in a solute/osmotic diuresis. Urine osmolality of a solute/osmotic diuresis is usually 300 to 500 mOsm/kg. A urine osmolality of 150 to 300 mOsm/kg indicates mixed diuresis.

A period of observation is recommended when the vital signs, electrolytes and mental status are normal. Serum chemistry panels should be followed at least daily until resolution of the diuresis and more frequently if the urine output is high (>3 L). Electrolytes should be corrected as needed. A higher level of care, including more frequent checks of vital signs and serum chemistry panels, should be considered for patients with poor mental status, significant volume overload or other abnormalities. Special consideration should also be given to patients with high urine outputs (>5 to 6 L daily). If the high urine output is associated with pathological diuresis, the patient will be more likely to manifest concerning volume or electrolyte abnormalities and, therefore, merit closer monitoring.

A stable patient with normal electrolytes should have access to oral fluids with replacement regulated by thirst. Intravenous fluids are generally avoided in this scenario to prevent continued diuresis unless the patient is unable to safely and reliably take oral fluids.

It is difficult to predict in which patients POD will develop given conflicting results from existing studies. In a study of chronic retention POD did not correlate with initial or post-drainage creatinine values.[8] In a review of 22 patients with POD those with severe renal impairment, fluid overload and central nervous system symptoms were at higher risk for diuresis.[7] A more contemporary study found that predictors of POD were higher serum creatinine, higher serum bicarbonate and urinary retention.[9]

Data on the duration of POD are limited but in a retrospective human study POD began a median of 3 hours (range 0 to 27 hours) after relief of the obstruction and lasted 1.8 days (range 0.4 to 12.5 days) with diuresis of 7 L (range 4 to 15 L) for the first 24 hours followed by decreasing urine output.[9] Once signs of the post-obstructive diuresis resolve and values are back to baseline, the patient can be considered for discharge home and further management as an outpatient.

Iatrogenic diuresis. As mentioned, it is recommended that stable patients with good mental status be allowed access to oral fluids, which enables them to self-regulate volume status. Intravenous fluids are avoided in this setting as the continued infusion of fluids can prolong the diuresis since the kidneys must manage this additional fluid load. When IV fluids are indicated, the infusion rate should be closely monitored and adjusted to prevent excessive replacement leading to a continued diuresis.

Pathological diuresis. Occasionally, patients undergo an excessive loss of water and electrolytes leading to derangements in blood chemistry and volume status, known as pathological diuresis. As discussed previously, obstruction has been shown to be associated with decreased expression of aquaporins. Although this decrease has been shown to be reversed with relief of obstruction, a decreased expression of aquaporin 1 persisted after 30 days.[33] After release of BUO, the fractional excretion of sodium may be significantly increased, even by as much as 20 times.[31] The increased activity of atrial natriuretic peptide also contributes to profound diuresis[46] and a decreased ability to acidify the urine.

Since POD can result in either water or solute diuresis, patients need to be closely monitored for hypovolemia and the clinical manifestations of electrolyte abnormalities, such as hypokalemia and hyponatremia or hypernatremia, depending on how much water is lost with the solutes. **IV fluids should be administered to those who are unable to tolerate oral fluids, those with poor mental status and in the setting of hypotension. The type of fluid used depends on the volume and sodium status. A guide to selecting replacement fluids for POD is summarized in figure 2.**

Volume status can be one of the hardest findings to assess on exam. To simplify the approach, blood pressure can be used as the marker of volume status (although this is by no means a perfect surrogate). In general, in patients with a normal volume status (normal blood pressure) fluid replacement with free water should be considered if there is a water diuresis (suggested by

BP	Na^+	Fluid Recommendation
N or ↑	N	Oral fluid
N or ↑	↑	Free water (Oral or IV)[a]
↓	N or ↓	0.9% saline
↓	↑	0.9% saline or 0.45% saline[b]

BP = Blood pressure; Na^+ = sodium; N = normal; ↑ = increased; ↓ = decreased, IV = intravenous

[a] This is likely a water diuresis and urine osmolality would be suspected to be low.

[b] 0.9% saline is preferred if volume status clearly hypovolemic. 0.45% saline provides water and sodium, allowing properly functioning (recovering) kidneys the opportunity to retain or excrete water or sodium as needed.

Figure 2. Guide to fluid selection in post-obstructive diuresis.

hypernatremia and a low urine osmolality). Water can be given orally or intravenously. Caution should always be taken to avoid correcting sodium alterations too rapidly. If hypovolemia is present, as evidenced by low blood pressure, 0.9% saline is usually the fluid of choice. If the volume deficit is not severe, 0.45% saline can also be used (particularly if hypernatremia is present) to provide sodium and water to help the kidneys maintain homeostasis. Sometimes it is recommended that urine output be replaced with 0.5 ml fluid per 1 ml urine. While this may help prevent hypovolemia, it can also propagate the diuresis if the fluid replacement is inappropriately high for the patient. As a result, the rate of fluid replacement should be closely monitored and adjusted depending on the clinical status (volume status and electrolytes) and urine output of the patient. Hypokalemia can occur and lead to life threatening arrhythmias if severe. As a result, potassium should be replaced aggressively, particularly if renal function is improving. Other electrolyte abnormalities should be corrected as well.

Pharmacological treatments. Alteration of post-obstructive diuresis through pharmacological mechanisms has been examined in animal models. Aquaporin expression was improved by administration of cyclooxygenase-2 inhibitors and associated with reduced urine output in the acute phase of POD but not after 24 hours.[47] Phosphodiesterase type 5 inhibition has been shown to induce aquaporin membrane insertion.[48] Some interventions focus on preventing the long-term consequences of obstruction, such as fibrosis. For example, in rodent UUO models treatment with statins, erythropoietin or rotenone decreased renal fibrosis.[49] **However, definitive human data are lacking to support routine pharmacological intervention for POD at this time.**

CONCLUSION

There are many causes of obstructive uropathy. A basic understanding of the resulting physiological changes of urinary obstruction helps with management of the post-obstructive diuresis that may be seen with the relief of the obstruction.

Appendix. Acquired causes of obstructive uropathy

Upper Urinary Tract	Lower Urinary Tract
Intraluminal process:	Intraluminal process:
Nephrolithiasis	Blood clot
Blood clot	Bladder/urethral stone
Fungus ball	Intramural process:
Sloughed papillae	Benign prostatic hyperplasia
Intramural process:	Urethral stricture
Ureteral stricture	Neoplasm:
Neoplasm:	Urothelial carcinoma
Urothelial carcinoma	Prostate carcinoma
Renal cell carcinoma	Metastasis
Metastasis	Infection:
Infection:	Prostatitis
Tuberculosis	Paraurethral abscess
Schistosomiasis	Functional:
Sarcoidosis	Neurogenic bladder
Extramural process:	Medication effect
Neoplasm:	Extramural process:
Abdominal tumor	Neoplasm:
Retroperitoneal tumor	Penile carcinoma
Metastasis	Pelvic tumor
Vascular:	Metastasis
Renal artery aneurysm	Phimosis
Abdominal aortic aneurysm	Trauma:
Retroperitoneal fibrosis	Hematoma
Retroperitoneal lymphadenopathy	Urinoma
Pregnancy	
Trauma:	
Hematoma	
Urinoma	

1. IMRT in Urology

Principles

- Intensity-modulated radiotherapy (IMRT) is an advanced mode of for delivering conformal EBRT which can be applied with or without image-guided radiotherapy (IGRT). IMRT is considered the gold standard for EBRT.
- IMRT is high-precision radiotherapy delivery that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor.
- IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the **tumor** by modulating or controlling the **intensity** of the radiation is delivered in **multiple beams in from various directions.** The intensity of each beam's radiation dose is dynamically varied according to treatment plan.
- IMRT also **allows higher radiation doses** to be focused to regions within the tumor while minimizing the dose to surrounding normal critical structures.
- Treatment is carefully planned by using 3-D computed tomography (CT) or magnetic resonance (MRI) images of the patient in conjunction with computerized dose calculations to determine the dose intensity pattern that will best conform to the tumor shape. Typically, combinations of multiple intensity-modulated fields coming from different beam directions produce a custom tailored radiation dose that maximizes tumor dose while also minimizing the dose to adjacent normal tissues.
- Because the ratio of normal tissue dose to tumor dose is reduced to a minimum with the IMRT approach, higher and more effective radiation doses can safely be delivered to tumors with fewer side effects compared with conventional radiotherapy techniques.

Pros and cons

- IMRT also has the potential to reduce treatment toxicity, even when doses are not increased.
- Due to its complexity, IMRT does **require slightly longer daily treatment times** and **additional planning** and safety checks before the patient can start the treatment than conventional radiotherapy.

In urology

- IMRT is used for treatment of prostate cancer in urology where it is combined with ADT both for N0 and N+ve disease.

- Dose is 65-86 Gy. Mostly >78 Gy is given.

Procedure

- Full course of RT is given by IMRT in multiple fractionated treatment sessions.
- In determining the total number of IMRT sessions and radiation dose, the oncologist considers the location and size of the tumor, doses to critical normal structures, as well as the patient's health.
- Typically, patients are scheduled for IMRT sessions **five days a week for five to eight weeks.**
- At the beginning of the treatment session, the therapist positions the patient on the treatment table, guided by the marks on the skin defining the treatment area. If molded devices were made, they will be used to help the patient maintain the proper position. The patient may be repositioned during the procedure. Imaging systems on the treatment machine such as x-ray or CT may be used to check positioning and marker location. Treatment sessions usually take between 10 and 30 minutes.

- With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT.

Side effects

- Main S/E of concern are related to radiation delivery to rectum and bladder:
  - Radiation proctitis, diarrhea, bowel perforation, rectourethral fistula
  - Radiation cystitis, irritative LUTS, hematuria
- General S/E
  - Nausea and vomiting
  - Skin changes→ Edema, induration, ulceration and blistering, discolouration
- Secondary cancer

2. Tissue engineered autologous urethra in reconstruction

- Various strategies have been proposed over the years for the regeneration of urethral tissue.
  - Woven meshes of PGA without and with cells
  - **Naturally derived collagen-based acellular (non-seeded) materials** such as bladder-derived acellular submucosa, small intestine deived submucosa (SIS), acellular urethral submucosa, and collagen gels
  - Seeded collagen matrices
- Acellular matrices
  - The acellular collagen-based matrix eliminated the necessity of performing additional surgical procedures for graft harvesting, and both operative time and the potential morbidity from the harvest procedure were decreased.
  - The bladder submucosa matrix (using human bladder acellular collagen matrices) proved to be a suitable graft for repair of urethral defects in patients with **failed hypospadias** reconstruction. However, a healthy urethral bed was needed for successful urethral reconstruction using acellular collagen-based grafts.
  - Tubularized non-seeded (acellular) small intestinal submucosa (SIS) has been used for **urethral stricture** repair.
  - Accellular matrices when used in tubularized urethral repairs, adequate urethral tissue regeneration may not achieved leading to fibrosis, graft contracture and stricture formation. This is because that tissue defects greater than 1 cm in a matrix without cells, usually heals with increased collagen deposition, increased fibrosis, and scar formation. On the other hand, cell-seeded matrices can fill larger defects without initiating fibrosis. V**ery large defects, greater than 30 cm, can be successfully treated using cell-seeded scaffolds.**
- Cellular matrices (Cell-seeded)
  - Autologous **rabbit bladder epithelial and smooth muscle cells** have been used for seeding the collagen matrices to ensure adequate tissue regeneration. This has been used clinically for long urethral stricture reconstruction as tubularized tissue-engineered urethra with good results.
  - Similarly tissue-engineered autologous urethra using **oral mucosa fibroblasts and keratinocytes seeding in cadaveric dermis** has been employed in BXO related strictures, with poor results.
  - Other cell types have also been tried experimentally in acellular bladder collagen matrices, including **foreskin epidermal cells and oral keratinocytes.**

- **SUMMARY**
  - Non-seeded matrices (acellular) are able to replace urethral segments when used in an **onlay** fashion.
  - If a tubularized urethral repair is needed, the matrices need to be seeded with autologous cells to avoid the risk of stricture formation and poor tissue development.

3. ATN

- The majority of all hospital-acquired AKI is secondary to ATN
- Renal hypoperfusion and renal ischemia are the most common causes of ATN, although nephrotoxic insults are also being recognized with increasing frequency.
- Exogenous nephrotoxic compounds
  - Antibiotics
  - Contrast media
  - Anesthetic agents
  - Diuretics
  - Chemotherapy
  - Immunosuppresive drugs
  - Analgesics
  - Heavy metals & poisons
  - Recreational drugs
  - Organic solvents and chemicals
- Endogenous nephrotoxic compounds
  - Pigment Nephropathy
    - Myoglobin, Hb, Methemoglobin
  - Intrarenal Crystal Deposition
    - Uric acid, Calcium, Oxalate
  - Tumor-Specific Syndromes
    - Tumor lysis syndrome
    - Plasma cell dyscrasias (myeloma kidney)
- Natural history
  - Oliguric phase usually begins less than 24 hours after the inciting incident and may last for 1 to 3 weeks. Urine volume averages 150 to 300 mL/day. The oliguric phase may be prolonged in the elderly. During this phase, the clinician must be alert for the expected complications, with special emphasis on metabolic consequences, gastrointestinal bleeding, and infection.
  - Diuretic phase is characterized by a progressive increase in urine volume, a harbinger of renal recovery. However, the SCr may continue to rise for another 24 to 48 hours before it reaches a plateau and falls. Severe polyuria during this phase is seen less frequently now. Careful management during this phase is crucial because up to 25% of deaths with AKI may occur in this phase.
- **Pathophysiology**
  - **The sentinel biochemical event in renal ischemia is the depletion of ATP**
  - **ATP depletion results in impaired function of the plasma membrane and intracellular ATP dependents enzymes/transporters leading to oxidative stress during reperfusion after ischemia, which is associated with cellular damage**

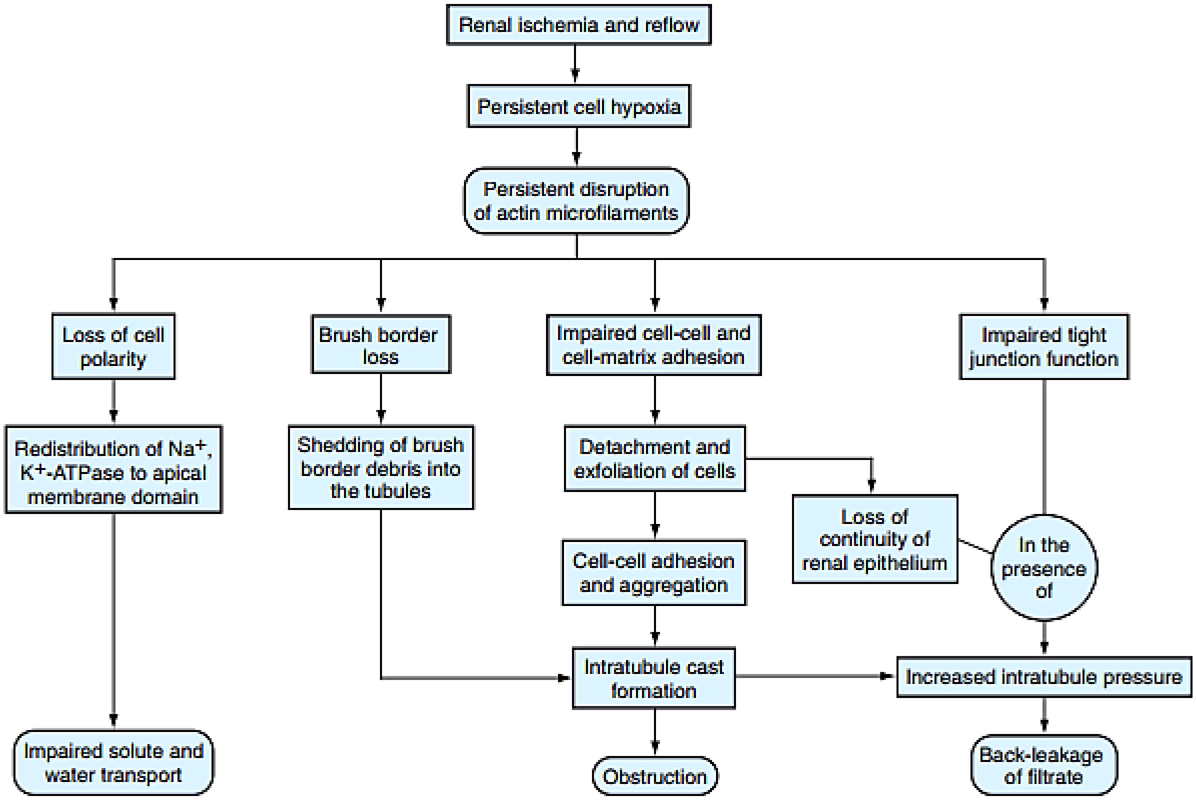
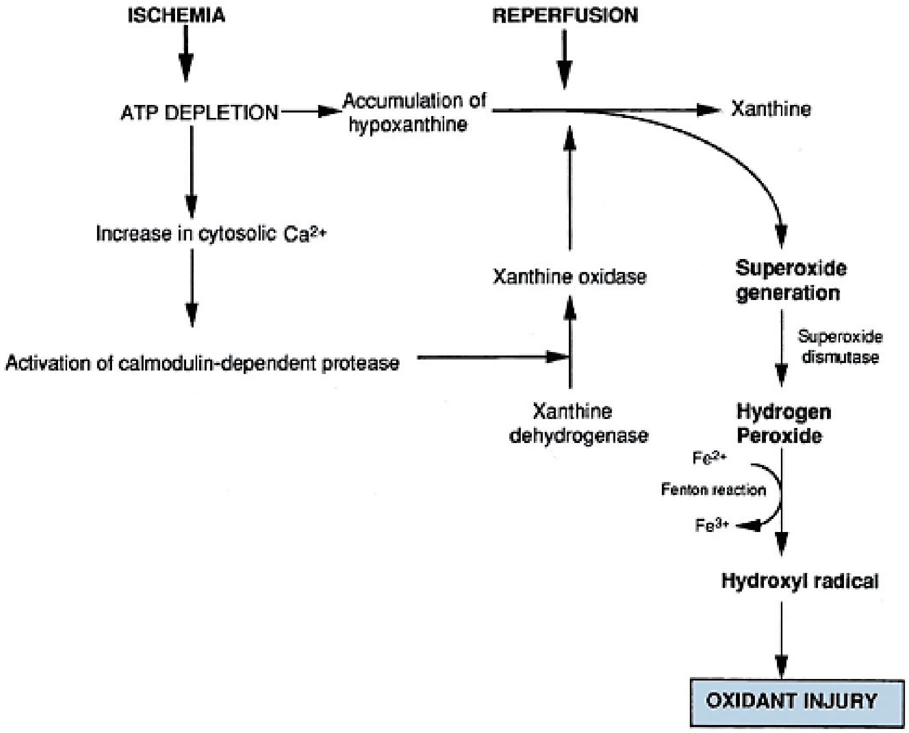

Renal ischemia and reflow
Persistent cell hypoxia
Persistent disruption of actin microfilaments
Loss of cell polarity
Brush border loss
Impaired cell-cell and cell-matrix adhesion
Impaired tight junction function
Redistribution of Na^+, K^+-ATPase to apical membrane domain
Shedding of brush border debris into the tubules
Detachment and exfoliation of cells
Loss of continuity of renal epithelium
In the presence of
Cell-cell adhesion and aggregation
Intratubule cast formation
Increased intratubule pressure
Impaired solute and water transport
Obstruction
Back-leakage of filtrate

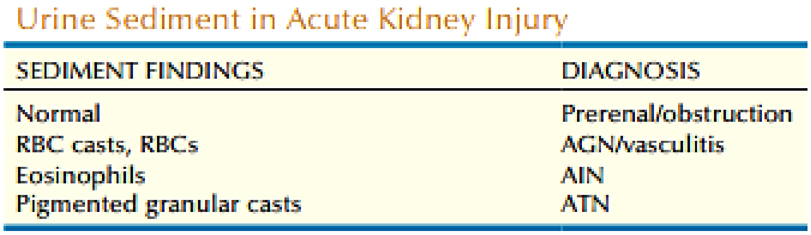
Figure 43–1. Pathophysiology of ischemic acute renal failure. The profound reduction in glomerular filtration rate associated with renal ischemia is due to a combination of intrarenal hemodynamic alterations and tubular epithelial injury leading to tubular obstruction and back-leakage of glomerular ultrafiltrate filtrate. (From Brady HR, Brenner BM, Lieberthal W. Acute renal failure. In: Brenner BM, editor. Brenner & Rector's the kidney. Philadelphia: WB Saunders; 1996. p. 1200–52.)

- **Pathophysiology of reperfusion injury**



16.

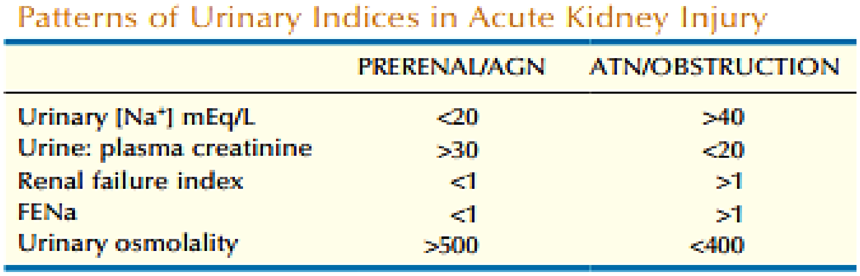
- **Evaluation**
  - Hb, Creat, urea, BUN, Sr. electrolyte
  - Urinalysis



Urine Sediment in Acute Kidney Injury

SEDIMENT FINDINGS	DIAGNOSIS
Normal	Prerenal/obstruction
RBC casts, RBCs	AGN/vasculitis
Eosinophils	AIN
Pigmented granular casts	ATN

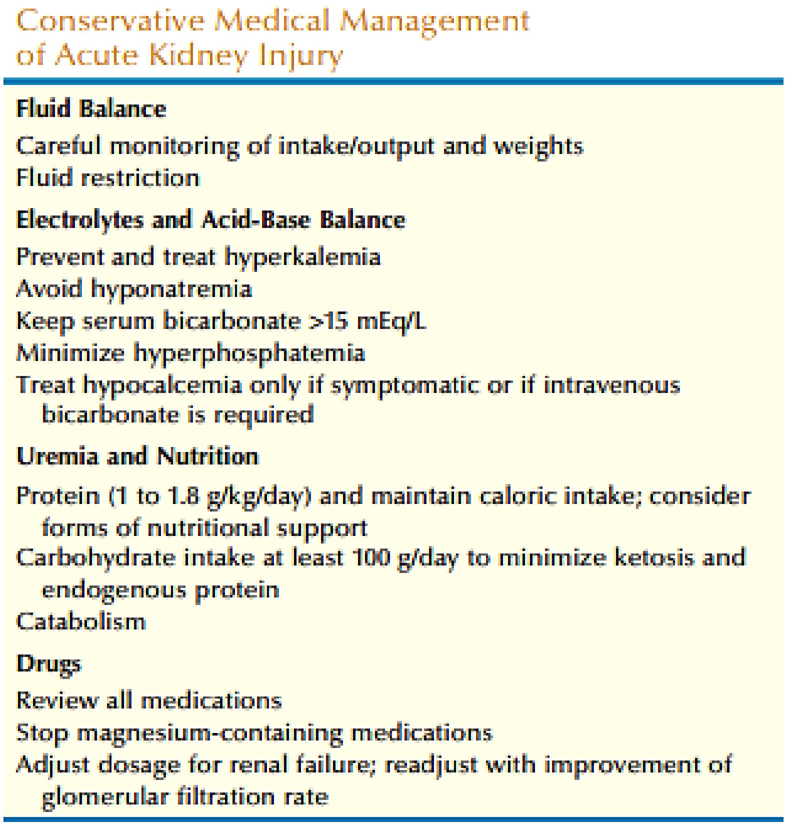
  - Fractional excretion of Na, Renal failure index



Patterns of Urinary Indices in Acute Kidney Injury

	PRERENAL/AGN	ATN/OBSTRUCTION
Urinary $[Na^+]$ mEq/L	<20	>40
Urine: plasma creatinine	>30	<20
Renal failure index	<1	>1
FENa	<1	>1
Urinary osmolality	>500	<400

  - Imaging: USG, X-ray, MAG-3/DTPA
- **Management**
  - **General**



Conservative Medical Management of Acute Kidney Injury

Fluid Balance
Careful monitoring of intake/output and weights
Fluid restriction
Electrolytes and Acid-Base Balance
Prevent and treat hyperkalemia
Avoid hyponatremia
Keep serum bicarbonate >15 mEq/L
Minimize hyperphosphatemia
Treat hypocalcemia only if symptomatic or if intravenous bicarbonate is required
Uremia and Nutrition
Protein (1 to 1.8 g/kg/day) and maintain caloric intake; consider forms of nutritional support
Carbohydrate intake at least 100 g/day to minimize ketosis and endogenous protein
Catabolism
Drugs
Review all medications
Stop magnesium-containing medications
Adjust dosage for renal failure; readjust with improvement of glomerular filtration rate

  - Both loop diuretics and mannitol administrationhave been proved to minimize the degree of renal injury if given at the time of the ischemic insult.
  - Mannitol and dopamine also used to increase urine output

4. Sterilization of endoscopic instruments

STERLIZATION: Steps in sterilization of endoscopic instruments

1) Dismantling
2) Pre-cleaning and cleaning
3) Drying
4) Packaging
5) Loading
6) Sterilization
7) Storage and monitoring

METHODS

- **Steam**
  - Most common and least expensive method of sterilization.
  - However, many lensed endoscopic instruments cannot be steam sterilized.
  - Even instruments and telescopes marketed as "autoclavable" will last longer if processed by alternative methods.

- **Ethylene oxide (ETO) gas**
  - Has been the standard for sterilizing heat-sensitive items, including endoscopes.
  - Sterilization cycles are typically one and one-half to two hours at 55°C.
  - Items must then be aerated mechanically for eight to 12 hours.
  - ETO is being gradually replaced in some hospitals with other sterilization methods, such as vapor-phase methods and paracetic acid because of cost and safety concerns.
  - However, caution should exercised before eliminating EO, since some of the alternatives have significant processing limitations and materials compatibility issues, including device lumen size (that can be sterilized) or lack of storage life of the devices (just-in-time sterilization)

- **Steris System**
  - Gamma irradiation is used for various disposable product sterilization
  - Radioisotope Cobalt 60 releases high-energy photons that ionize the irradiated material

- **Per-acetic acid**
  - Used in a liquid processor to sterilize items in less than 30 minutes at 50-55°C.
  - This method is a just-in-time process and sterility cannot be maintained for long term storage.

- **Plasma and/or vapor phase sterilizers**
  - Sterrad (Advanced Sterilization Processes of Irvine, Calif) is FDA-approved for this use in the United States.

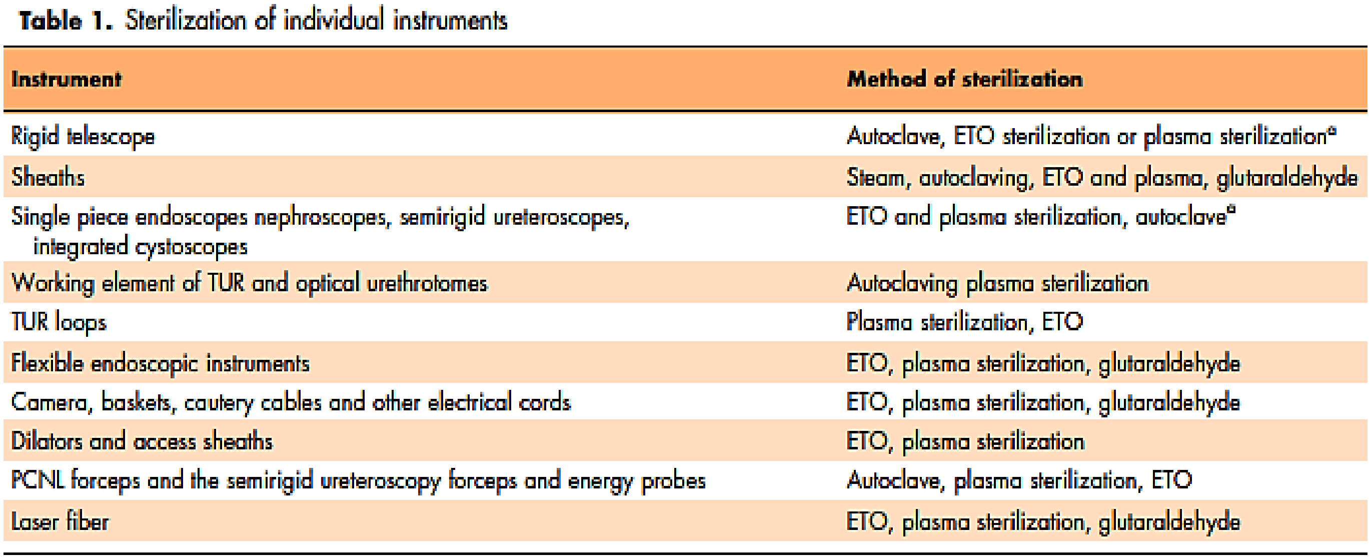


Table 1. Sterilization of individual instruments

Instrument	Method of sterilization
Rigid telescope	Autoclave, ETO sterilization or plasma sterilization[a]
Sheaths	Steam, autoclaving, ETO and plasma, glutaraldehyde
Single piece endoscopes nephroscopes, semirigid ureteroscopes, integrated cystoscopes	ETO and plasma sterilization, autoclave[a]
Working element of TUR and optical urethrotomes	Autoclaving plasma sterilization
TUR loops	Plasma sterilization, ETO
Flexible endoscopic instruments	ETO, plasma sterilization, glutaraldehyde
Camera, baskets, cautery cables and other electrical cords	ETO, plasma sterilization, glutaraldehyde
Dilators and access sheaths	ETO, plasma sterilization
PCNL forceps and the semirigid ureteroscopy forceps and energy probes	Autoclave, plasma sterilization, ETO
Laser fiber	ETO, plasma sterilization, glutaraldehyde

DISINFECTANTS

1. Formalin
2. Sodium hypochlorite
3. Hydrogen peroxide
4. Adverse effects of residual particles applicable to formalin

FORMALIN

- Water-based solution containing 37% formaldehyde is called formalin
- Bactericide, tuberculocide, fungicide, virucide and sporicide

Mode of Action

– Formaldehyde inactivates microorganisms by alkylatingthe proteins and purinebases of DNA

Formalin- *role as disinfectants*

- To sterilize surgical instruments, especially when mixed with ethanol.
- To disinfect the dialysis machines
- In vapour or gas form, to disinfect the sealed portion of the cabinet, endoscopes, small glass/plastic equipments kept in boxes

Adverse effects

- Handling persons can have:
  - watery eyes
  - burning sensations in eyes, nose, and throat
  - Coughing, wheezing, nausea
  - skin irritation
- Thus its use is limited by its irritating fumes and its pungent odor

Adverse effects of residual particles applicable to formalin

- Formalin's role has been suspected human carcinogen
- It has been linked to nasal cancer and lung cancer
- Chronic exposure can cause adverse effects on testis, sperm formation and sperm viability

SODIUM HYPOCHLORITE

- NaOCl
- 5% Solution in water- commonly called "Bleach"
- Acts as a strong oxidizing agent
- Effective against bacteria, viruses and fungi

Uses

- Sodium hypochlorite can be effectively used for water purification
- On a large scale- used for surface purification, bleaching, odorremoval etc.

NaOCl- Advantages

- Can be easily and safely stored and transported
- Broad spectrum of antimicrobial activity
- Do not leave toxic residues on surfaces
- Not affected by water hardness
- Cheap/inexpensive
- Fast acting
- Remove dried or fixed organisms and biofilms from surfaces
- Low incidence of serious toxicity

NaOCl- Disadvantages

- Although low toxicity, but it is a dangerous and corrosive substance
- Safety measures needed to protect workers and the environment
- It should not come in contact with air, because this will decompose it, and its efficacy is lost.
- Gets inactivated in the presence of blood. So, surfaces with large amount of blood need to be cleaned of blood before disinfection with NaOCl
- Does not deactivate Giardia Lambiaand Cryptosporidium

HYDROGEN PEROXIDE (H_2O_2)

- Oxidizing Agent
- Potent and broad spectrum of antimicrobial activity against almost all microorganisms
- Act by denaturing the proteins and lipids of microorganisms
- Effective for disinfecting hard surfaces and equipment
- Relatively safe but may irritate skin and damage clothing when concentrated
- At a 5-20% concentration, it is considered bactericidal, virucidal(non-enveloped viruses may be resistant), and fungicidal
- At high concentrations it can destroy spore also

- However, activity against mycobacteria is limited
- Used in both liquid and gas form for preservative, disinfection and sterilization
- Flexibility in use, and safety profile in comparison to other microbiocidesis the major advantage

5. **Lycopenes uses in Urology**
   - Lycopene is a phytochemical that belongs to a group of pigments known as carotenoids. It is red, lipophilic and naturally occurring in many fruits and vegetables, with tomatoes and tomato-based products containing the highest concentrations of bioavailable lycopene.

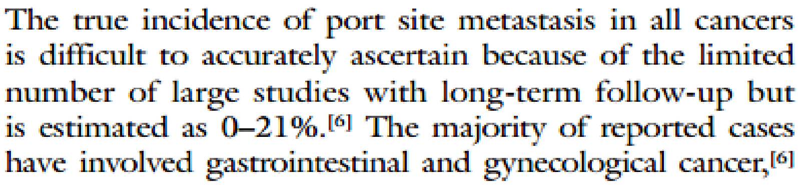
   - **Urological applications**
   - Prevention of prostate cancer
   - Male infertility
   - Prostate health and prostatitis
   - Might help protect against side-effects caused by the drug doxorubicin which specifically damaging to the developing sperm cells

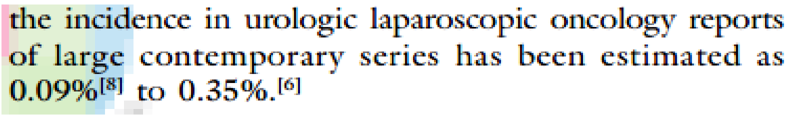
   Mechanism
     - Excessive amounts of reactive oxygen species (ROS) cause a state of oxidative stress, which result in sperm membrane lipid peroxidation, DNA damage and apoptosis, leading to decreased sperm viability and motility. Elevated levels of ROS are a major cause of idiopathic male factor infertility
     - Lycopene, the most potent singlet oxygen quencher of all carotenoids, is a possible treatment option for male infertility because of its antioxidant properties.
     - Prevention of DNA damage and carcinogenesis in PCa prevention
     - Mediate cell cycle arrest in cancer cells
     - Impairs Tumour Cell Proliferation and Growth
     - **Potential to induce apoptosis in cancer cells**
     - Lycopene is able to decrease the serum PSA-levels in patients with prostate hyperplasia or cancer, demonstrating its effect on proliferating prostate cells

6. **Complications of chemotherapy in Urology**
   - Systems affected:
     - Hematological- Bone marrow depression, pancytopenia
     - Gastrointestinal- nausea, vomiting, diarrhea
     - Gonadal- Low testosterone, loss of libido, ED, infertility
     - Ototoxicity
     - Renal- AKI, CKD, GN
     - Neurological- Neuropathy
     - Pulmonary fibrosis
     - Cardiac toxicity
     - Immunosuppresion
     - Increased propensity of infection
   - The late complications associated with cisplatin-based chemotherapy include secondary malignancies, cardiovascular disease, avascular necrosis, and cognitive impairment.
   - Risk of metabolic syndrome

- Complications of Intravesical chemotherapy
    - Dysuria, prostatitis
    - Cystitis
    - Bladder cancer
    - Gross hematuria
    - UTI
    - Bladder perforation

7. **Port site metastases (PSM)**
    - **Rare**


The true incidence of port site metastasis in all cancers is difficult to accurately ascertain because of the limited number of large studies with long-term follow-up but is estimated as 0–21%.[6] The majority of reported cases have involved gastrointestinal and gynecological cancer,[6]


the incidence in urologic laparoscopic oncology reports of large contemporary series has been estimated as 0.09%[8] to 0.35%.[6]

- **Etiopathogenesis**
    - Natural tumor behaviour
    - Local wound factors including alteration of blood vessels and lymphatics of abdominal wall near the port site
    - Immune and stress response to laparoscopy and surgery
    - Direct seeding or implantation of tumor cells- Inoculation and aerosolizations to port sites
    - Systemic dissemination of tumor cells during handling of tumor intraoperatively

- **Prevention**
    - Avoid unnecessary handling of the tumor intraop
    - Use of specifically designed endobags for tumor extraction
    - Avoid tearing of endobag during extraction
    - Avoid tumor rupture ad spillage during extraction if endobag is available or not applied

- **Treatment**
    - Depends of primary malignancy, and degree local involvement
    - Solitary PSM without distant mets- Excision

8. **Urological manifestations of Diabetes (Friends→ Following are the headings)**
    - Soft tissue infection- Fournier
    - UTIs
    - Papillary necrosis and obstruction
    - Stone disease- UA (by lowering the urine pH, insulin resistance)
    - Hypocontractile bladder, Diabetic cystopathy
    - As a preoperative risk factor, and increased wound complications
    - Diabetic nephropathy, ESRD

OXIDATIVE STRESS AND INFERTILITY

Infertility- 15% of population, 40% male factor

30% of male infertility due to idiopathic oligoasthenoteratozoospermia (iOAT)

Definition: Necrosis of normal sperms, impaired motility and abnormal forms

Classification

- Mild (Normal counts but astheno + teratospermia)
- Moderate (counts between 5 and 20 million/ ml)
- Severe (counts <5 million/ ml)

History: Inability to conceive despite regular unprotected intercourse (3/ more per month X 1 year)

Examination: Normal genitalia and secondary sexual characteristics

Investigations:

Semen may show normal/ low counts, motile sperms <40%, normal sperms <4%

Normal/ low testosterone and inhibin. Normal/ high FSH, LH, estradiol

Increased markers of seminal oxidative stress: Chemiluminescence, flow cytometry, Isoprostane, nitroblue tetrazolium reduction

Aetiology

Aging

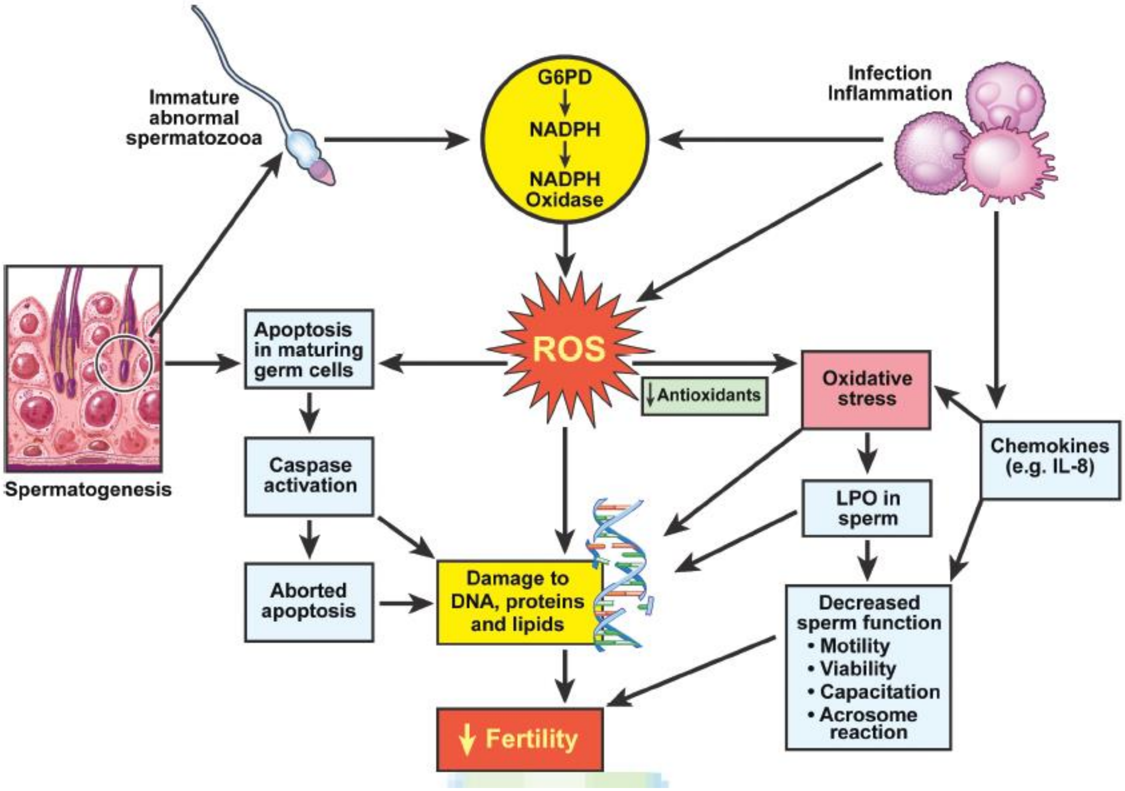
Functional alterations in epididymis causing DNA methylation and transcription inhibition

Infection: Herpes, Chlamydia, Adenovirus

Genetic (Autosomal recessive)

Pathogenesis

- ROS are involved in capacitation, acrosome reaction, gene and vascular tone regulation, prostaglandin metabolism. (ROS- Atleast one upaired electron in the molecule)
- Produced by immature gametes and leucocytes in response to external stress/ trauma
- Increase in reactive oxygen species
- Overwhelms antioxidants: Superoxide dismutase, glutathione peroxidase, zinc, tocopherol, ascorbate, beta-carotene, urate, ceruloplasmin
- Marker of lipid peroxidation is **Malondialdehyde (MDA)**- Semen levels increased in iOAT
- Spermatids and spermatozoa cell membrane rich in polyunsaturated lipids- Apoptosis, poor motility, abnormal DNA due to fragmentation
- Increased levels of Bax and low Bcl-2 leads to apoptosis and mitochondrial dysfunction



Treatment

No appreciable cause. Treat with hormones and anti-oxidants primarily to improve counts

Evidence for antioxidant therapy is sparse

Hormones

Tamoxifen blocks androgen receptors in hypothalamus- increased GnRH. Not effective

May be combined with Testosterone: Improved epididymal sperm motility, morphology and fertilization capacity

FSH: Mixed results

Carnitines

Water soluble antioxidant from diet (75%) or synthesised from Lysine and Methionine (25%)

Responsible for sperm motility: Spermatozoa show high L-Acetyl carnitine during epididymal transit

Used for beta oxidation of long chain fatty acids in sperm mitochondria

Restore phospholipid content of mitochondrial membrane, anti-oxidant, increases PGE2 in semen

3-4 gm OD for 2-4 months: Improved motility and morphology

NSAIDs

Semen in iOAT shows high prostaglandin levels

Low dose NSAIDs improves semen quality, higher doses impair semen quality

Can be used in combination with L-Acetyl carnitine

Vit C and E

Interrupts lipid peroxidation, Vit E a cofactor in various anti-oxidant enzymes

Oral Vit E reduced semen malondialdehyde and improved motility

Vit C concentration in semen is ten-fold higher than in plasma- reduces ROS levels

Believed to have synergistic action with Vit E

No benefit in prospective trials

Selenium

Essential for testicular development, spermatogenesis/ morphology and motility. Anti-oxidant

Co-factor for phospholipid hydroperoxide gluatathione peroxidase (PHGPX)

Se deficiency: Mid tail piece breaks, loss of motility, sperm head abnormalities

RCT: Improved motility and peroxidation markers when used with Vit E

NAC

Derivative of L-Cysteine

In vitro incubation with semen: Reduced ROS levels

Improves sperm concentration, motility and acrosome reaction

Zinc

Prevents peroxidation, DNA fragmentation and apoptosis

Zinc deficiency: Distorted flagella, absent mid-piece

Decreases seminal Bax, MDA, anti-sperm antibody titres and improves sperm parameters

66 mg OD $ZnSO_4$ usually combined with Folate 5 mg OD

Tranilast

Mast cell stabilizer: Decreased release of pro-inflammatory cytokines from macrophages

Increased levels of mast cells seen in seminiferous tubules in males with idiopathic infertility

200 mg OD for 3 months: Increased counts and motility

Lycopene

Carotenoid, free radical scavenger

200 mg BD for 3 months: Improved counts and motility

Pentoxifylline

Non-selective phosphodiesterase inhibitor, increases cAMP and reduces leucotrienes

Improves sperm motility. 400 mg BD

Adrenergic antagonists

MOA not known. Can improve counts

APPROACH TO AZOOSPERMIA

Of the men presenting for fertility investigation, up to 20% are found to be azoospermic after atleast two semen analysis. These men can be categorized as having:

1) Pre-testicular azoospermia (2%)
    Hypothalamic or pituitary abnormality- hypo-gonadotropic-hypogonadism, prolactinoma
2) Testicular failure or non-obstructive azoospermia (70%)
    a) Complete absence of spermatogenesis (Sertoli cell only syndrome)
    b) Maturation arrest
    c) Hypospermatogenesis
    d) AZF mutations
3) Post-testicular causes for azoospermia (28%)
    a) Obstruction: Epididymis, vas or ejaculatory ducts
    b) Ejaculatory dysfunction- Anejaculation or retrograde ejaculation (SCI, RPLND, TURP)

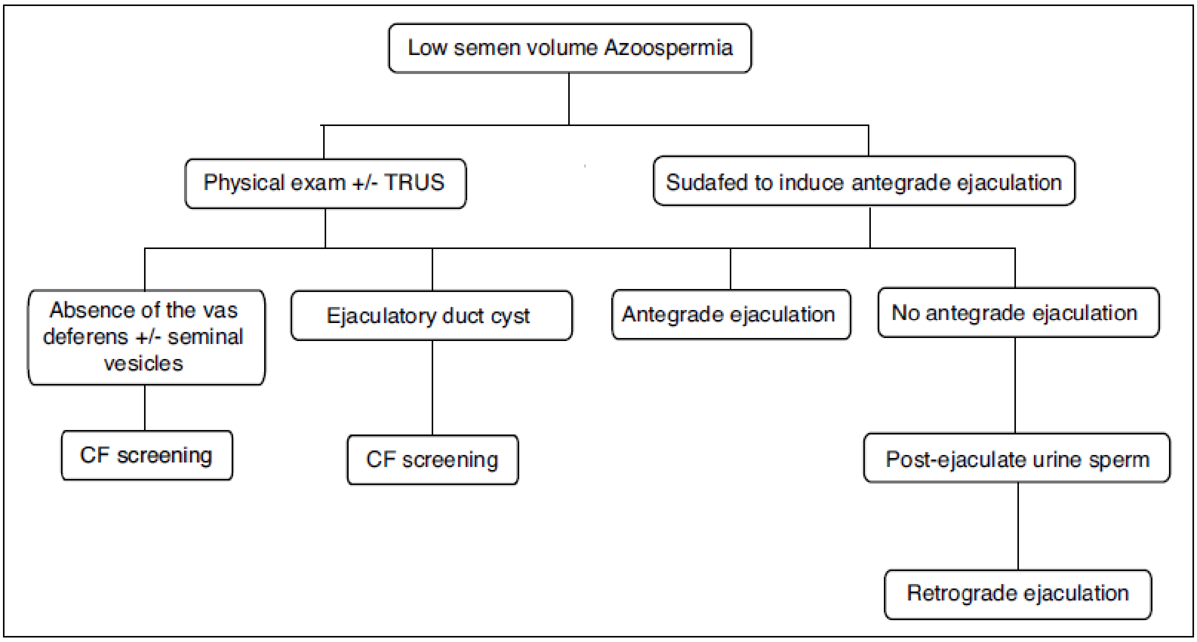
History

- General: Duration, primary/ secondary, libido, ED, PE, sexual activity
- Medical: DM, hypogonadism, pituitary pathology
- Infection: Mumps, TB, epididymo-orchitis
- Surgery: RPLND, orchidectomy, hydrocele, hernia, varicocoele, vasectomy, orchidopexy
- Drugs : Testosterone, antiandrogens, LHRH agonists/ antagonists, antipsychotics, chemo, alpha blockers and 5 ARI, marijuana, alcohol, pesticides, narcotics
- Genetic abnormalities

Examination

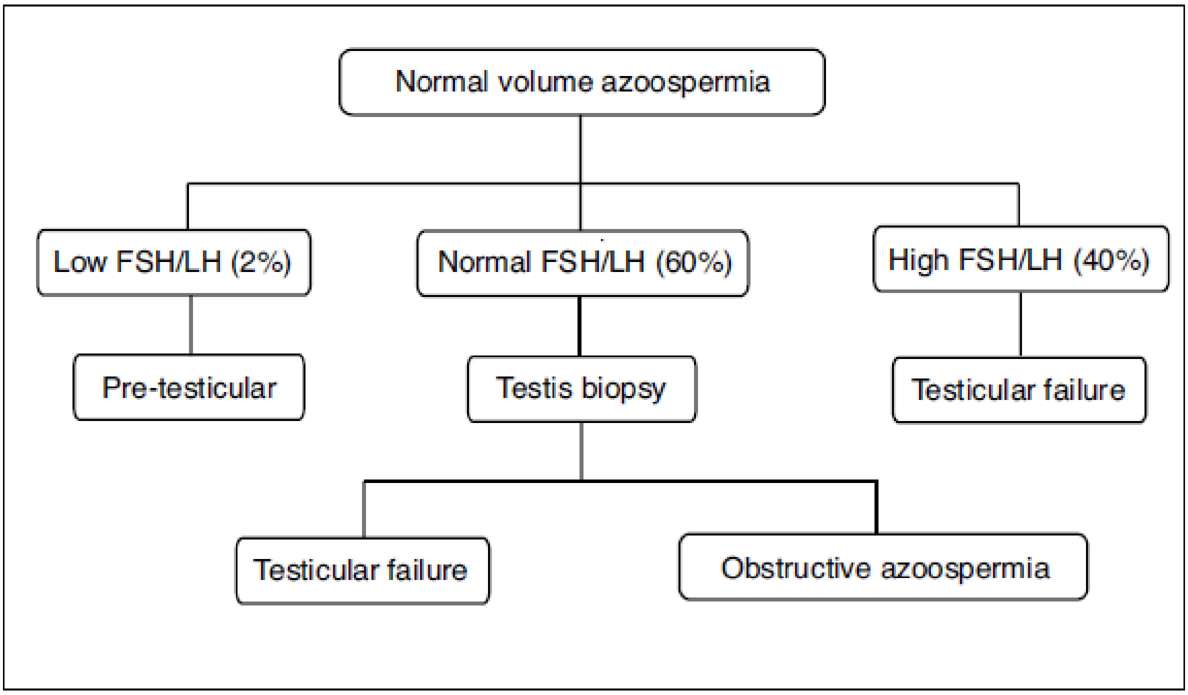
- Virilization
- Scars over abdomen, groin, genitalia
- Penile curvature, hypospadias, small penis
- Size of testes, presence of vas, epididymal induration, varicocoele
- Midline cyst or palpable seminal vesicle on DRE

Low volume azoospermia


Low semen volume Azoospermia
Physical exam +/- TRUS
Sudafed to induce antegrade ejaculation
Absence of the vas deferens +/- seminal vesicles
Ejaculatory duct cyst
Antegrade ejaculation
No antegrade ejaculation
CF screening
CF screening
Post-ejaculate urine sperm
Retrograde ejaculation

In low volume azoospermia without ejaculatory dysfunction, the seminal vesicles are always involved
Cystic fibrosis mutation: CBAVD (80%), ejaculatory duct obstruction/ cyst (25%)
In ejaculatory duct obstruction, the seminal vesicle is >1.5 cm in diameter
Absent vas- USG to look for absence of kidney on ispilateral side

Normal volume azoospermia



Hypogonadotropic hypogonadism: MRI, genetic
Testicular failure: Karyotype and Y chromosome microdeletion
Normal FSH/ LH and normal testes: Biopsy

In summary

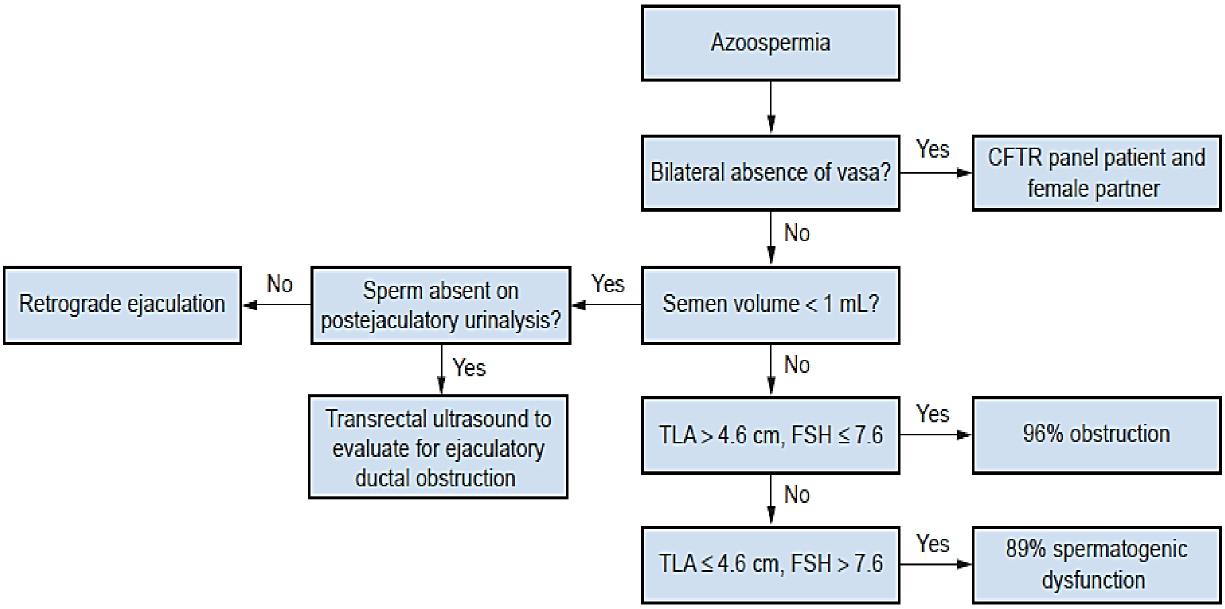

Azoospermia
Bilateral absence of vasa?
Yes
CFTR panel patient and female partner
No
Retrograde ejaculation
No
Sperm absent on postejaculatory urinalysis?
Yes
Semen volume < 1 mL?
Yes
Transrectal ultrasound to evaluate for ejaculatory ductal obstruction
No
TLA > 4.6 cm, FSH ≤ 7.6
Yes
96% obstruction
No
TLA ≤ 4.6 cm, FSH > 7.6
Yes
89% spermatogenic dysfunction

Figure 24-11. **Algorithm for evaluation of azoospermia. CFTR, cystic fibrosis transmembrane conductance regulator; FSH, follicle-stimulating hormone; TLA, testis longitudinal axis measured by caliper orchidometer.**

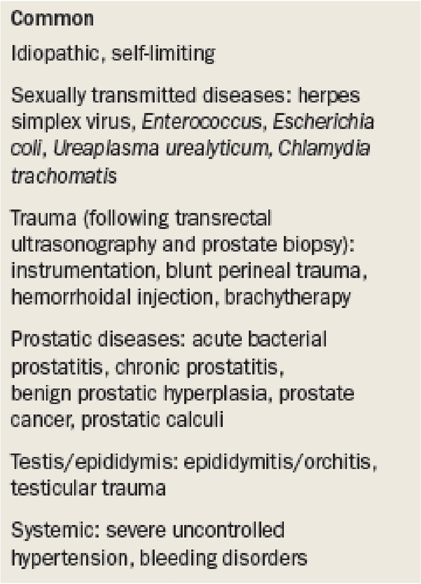
Management

Hypogonadism : beta HCG (5000 U thrice weekly) +/- human menopausal gonadotropin (75 U thrice weekly)/ subcutaneous GnRH pump (q2h) for 2 yrs (central)
: No specific therapy for Leydig cell failure, ICSI may be attempted
Sertoli cell only syndrome: Adoption/ donor insemination
Maturation arrest : Sperm extraction* and ICSI (* Covered in a separate answer)
Hypospermatogenesis : Same as above
AZFa and b mutation : Adoption/ donor insemination. AZFc mutation: Sperm extraction and ICSI
Karyotype abnormality : E.g. Klinefelter. ICSI

Epididymal obstruction : Vaso-epididyymostomy (85% patency and 50% pregnancy rates)
Vasal obstruction : Vaso-vasostomy (99% patency and 50% pregnancy)
CBAVD : CF mutation testing (including partner) and if -, ICSI. If +, counsel for adoption/ donor semen
Ejaculatory obstruction : TURED
Retrograde ejaculation : Alpha adrenergic agonists like Sudafed (Pseudoephedrine 120 mg BD)
Bladder sperm retrieval (Hydrate, NaHCO3 catheterize/ void into medium)
Anejaculation : Penile vibrator/ electro-ejaculation

HEMATOSPERMIA

- Peaks in 30-40 yrs age group
- Mostly benign <40 yrs. Older men, suspect malignancy
- Cause often unrecognized (68%)



Common

Idiopathic, self-limiting

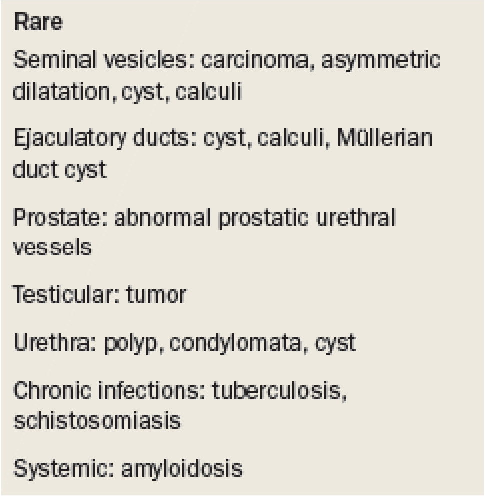
Sexually transmitted diseases: herpes simplex virus, *Enterococcus*, *Escherichia coli*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*

Trauma (following transrectal ultrasonography and prostate biopsy): instrumentation, blunt perineal trauma, hemorrhoidal injection, brachytherapy

Prostatic diseases: acute bacterial prostatitis, chronic prostatitis, benign prostatic hyperplasia, prostate cancer, prostatic calculi

Testis/epididymis: epididymitis/orchitis, testicular trauma

Systemic: severe uncontrolled hypertension, bleeding disorders



Rare

Seminal vesicles: carcinoma, asymmetric dilatation, cyst, calculi

Ejaculatory ducts: cyst, calculi, Müllerian duct cyst

Prostate: abnormal prostatic urethral vessels

Testicular: tumor

Urethra: polyp, condylomata, cyst

Chronic infections: tuberculosis, schistosomiasis

Systemic: amyloidosis

History and examination

- Fever, LUTS, genital trauma, TURP/ TRUS biopsy, HTN, bleeding disorders
- Blood at meatus/ in condom collected semen, genital and rectal exam

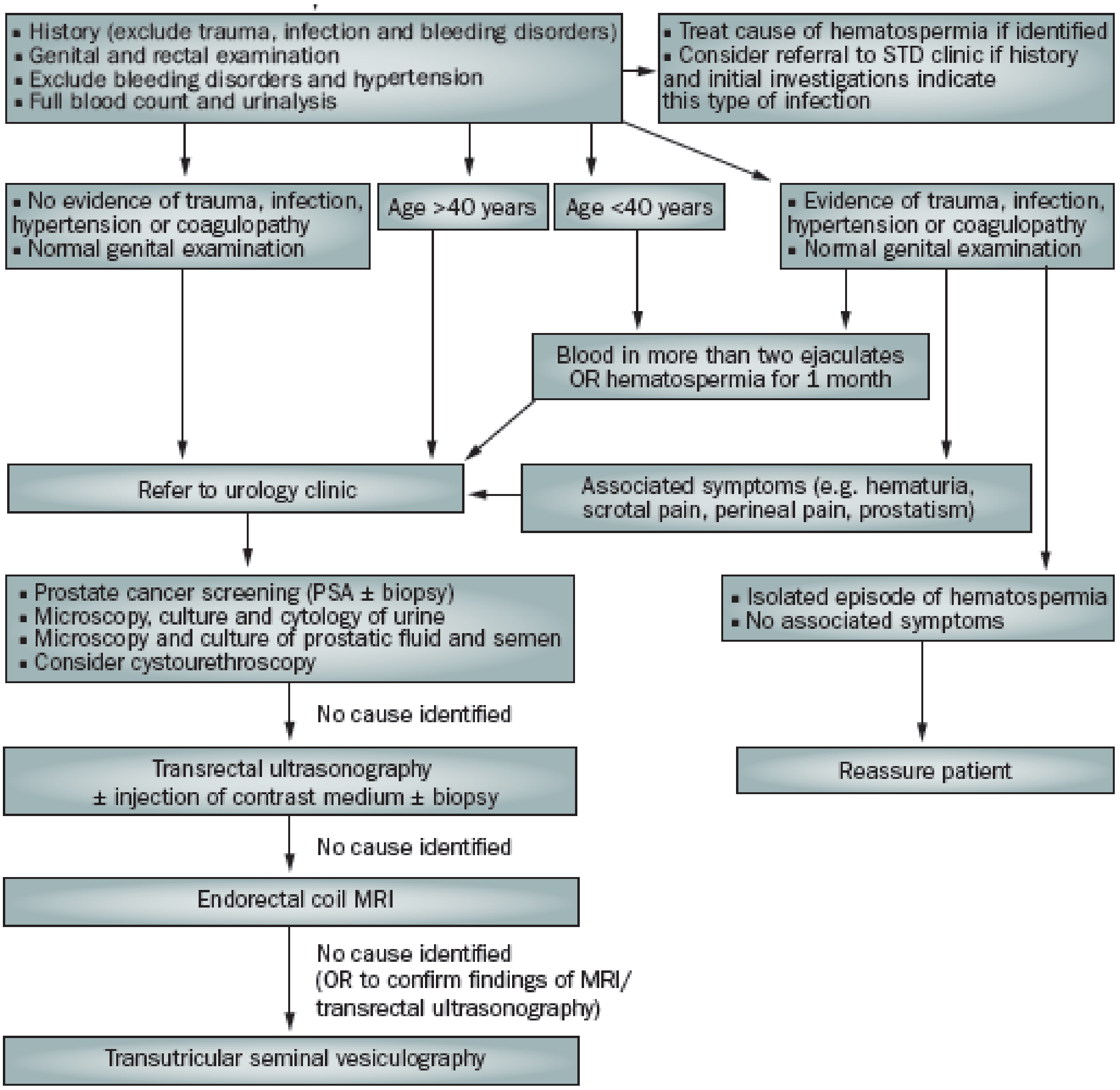
Investigations

- Complete blood count, coagulation profile, PSA
- EPS, urine routine, urine culture, semen analysis, semen culture
- Ultrasound KUB, KUB X ray
- Cytology, cystoscopy
- TRUS +/- biopsy, MRI with endorectal coil, seminal vesiculography

Management algorithm

Obstinate haematospermia with no obvious cause:

  - Endorectal heat via rotating magnet (80% success)
  - Seminal vesicle puncture and antibiotic irrigation (90% success)


▪ History (exclude trauma, infection and bleeding disorders)
▪ Genital and rectal examination
▪ Exclude bleeding disorders and hypertension
▪ Full blood count and urinalysis
▪ Treat cause of hematospermia if identified
▪ Consider referral to STD clinic if history and initial investigations indicate this type of infection
▪ No evidence of trauma, infection, hypertension or coagulopathy
▪ Normal genital examination
Age >40 years
Age <40 years
▪ Evidence of trauma, infection, hypertension or coagulopathy
▪ Normal genital examination
Blood in more than two ejaculates OR hematospermia for 1 month
Refer to urology clinic
Associated symptoms (e.g. hematuria, scrotal pain, perineal pain, prostatism)
▪ Prostate cancer screening (PSA ± biopsy)
▪ Microscopy, culture and cytology of urine
▪ Microscopy and culture of prostatic fluid and semen
▪ Consider cystourethroscopy
▪ Isolated episode of hematospermia
▪ No associated symptoms
No cause identified
Transrectal ultrasonography ± injection of contrast medium ± biopsy
Reassure patient
No cause identified
Endorectal coil MRI
No cause identified (OR to confirm findings of MRI/ transrectal ultrasonography)
Transutricular seminal vesiculography

SPERM RETRIEVAL TECHNIQUES

First described in 1988

Indications

- -Non-reconstructible obstructive azoospermia (epididymal, CBAVD, failed VV/ VE, extensive damage)
- -Non-obstructive azoospermia
  - Hypogonadism
  - Testicular failure (Sertoli cell only, hypospermatogenesis, maturation arrest)
  - AZFc mutation
  - Karyotype abnormalities: Klinefelter

No evidence to recommend one technique over another

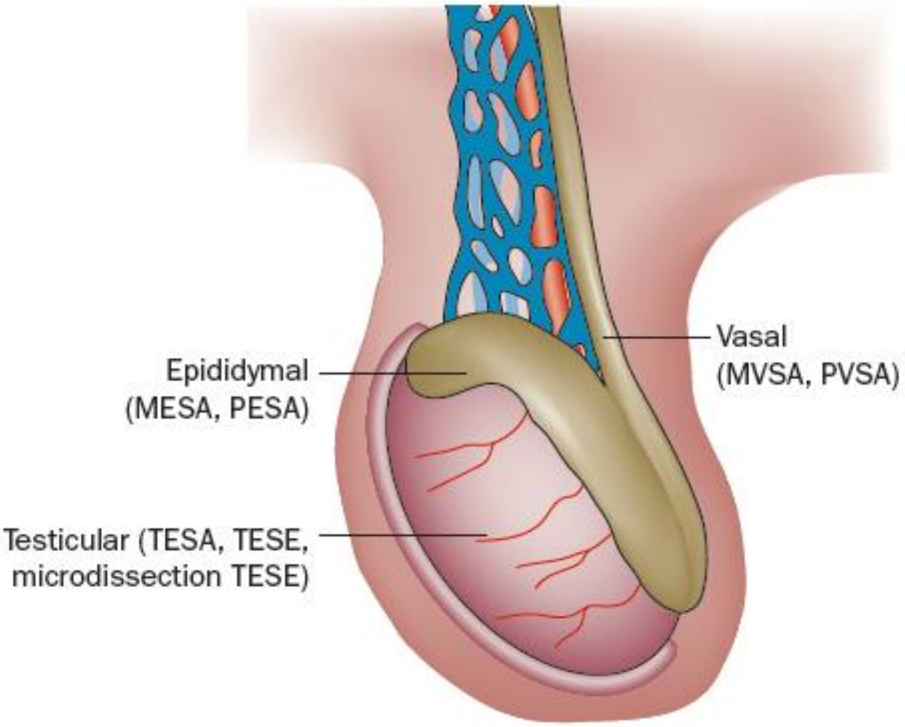


Figure 1 | Sites of sperm retrieval. Sperm retrieval is theoretically possible and commonly performed in three reproductive tract organs: the vas deferens, epididymis, and testicle. Abbreviations: MESA, microscopic epididymal sperm aspiration; MVSA, microscopic vasal sperm aspiration; PESA, percutaneous epididymal sperm aspiration; PVSA, percutaneous vasal sperm aspiration; TESA, testicular sperm aspiration; TESE, testicular sperm extraction. With kind permission from Springer Science+Business Media B. V. © Turek, P. J. in *Reproductive Endocrinology and Infertility: Integrating Modern Clinical and Laboratory Practice.* (eds Carrell, D. T. & Peterson, C. M.) 453–465 (Springer, 2010).

Vasal aspiration

MVSA

- Technique similar to vasography
- Local anaesthesia or using mild intravenous sedation in a no-scalpel manner.
- Vas deferens is secured through a scrotal puncture.
- Loupe or microscopic magnification, a small puncture or hemi-incision is made in the muscular wall
- 24 gauge syringe is used to aspirate the sperm-rich fluid until 2–20 million motile sperm collected.
- Applying pressure or massaging the testis vas deferens can help express fluid for aspiration.
- Wall is closed with microscopic sutures. Recovery is expected within 24
- Adverse effects including bleeding (<1%) and infection (<1%), vas stenosis (<5%)

PVSA

- Percutaneous approach, a 30 G needle is inserted into the vasal lumen through which fluid aspirated
- Main advantage of vasal sperm lies in the maturity of the sperm retrieved due to epididymal passage
- Sperm can be used not only for ICSI, but also for intrauterine insemination and IVF
- Well-suited for cryopreservation- High level of post-thaw viability and superior motility
- Can be timed to occur on same day as ovulation or frozen and thawed

Epididymal aspiration

- Patients in whom the vas deferens is either absent or obstructed
- Same day as partner ovulation, or retrieved sperm can be frozen

MESA

- Local anaesthesia, with or without light sedation
- (<1 cm) incision is made in the superior hemiscrotum overlying the caput, microscope used
- Dilated epididymal tubules individually incised or punctured, fluid aspirated until 2–10 million motile sperm are collected, and the overlying tunica is closed with microscopic sutures

PESA

- Testis is isolated, scrotal skin stretched taut over its upper pole.
- The caput epididymis is palpated, percutaneously punctured with a small-gauge butterfly needle until sufficient motile sperm are collected. If no sperm, several redirected passes made
- MESA more expensive but reliable with higher success rates. No risk of vasal stenosis
- Variable levels of maturation, less motility than vasal sperm.
- Best suited for ICSI, with good oocyte fertilization (60%) and pregnancy (50%) rates

Testicular retrieval

The successful use of ICSI with testicular sperm was first reported by Craft in 1993

TESA

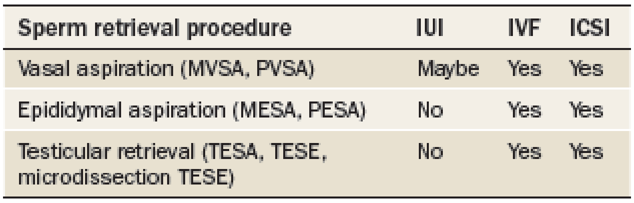
- Outpatient basis local +/- sedation. It can be timed to occur with oocyte harvest or in advance
- Stabilization of the testicle in the scrotal sac between the thumb, index, and middle fingers. A
- Butterfly needle or angiocath directed into parenchyma and aspirated with multiple passes
- Examine aspirate for sperms. Repeat/ sample other side as per need.
- Apply pressure over site of aspiration. Bleeding (1%) and infection (1%)

Percutaneous TESE

- Large gauge (16–18 gauge) needle or Biopty® gun, 14 gauge needle is used to obtain core biopsies
- Scrotal skin puncture by scalpel, the Biopty® needle is advanced through the skin and into the testicular tunica albuginea either at the lower or upper pole of the testicle and is directed parallel to the long axis of the testicle.
- After firing the Biopty® gun, the tissue core is placed in culture medium for processing.
- The main risk with testis tissue retrieval by Biopty® gun is haematoma, which occurs in 1–5%

Open TESE

- Testis and scrotum are stabilized and the scrotal skin incised with a 1 cm incision.
- The tunica vaginalis is opened and albuginea is incised parallel to the visible surface vessels. Testicular tissue is excised and further processed for ICSI. The tunica albuginea and scrotum are closed with absorbable sutures.
- The recovery period is 24–48 h risks are low infection (<1%), bruising, and bleeding (<5%). Addition of microscope improves yield. Esp important in Sertoli cell only, Klinefelter, AZFc
- Similarly, 18 point FNAC to identify areas of better yield provides higher retrieval rates in TESE. A plateau of approximately 60% detection rate is noted with ≥15 FNAC samples
- Sperm production in non-obstructive azoospermia testes can be focal. TESE more effective vs TESA 15-50% will have low testosterone at 1 year after TESE
- Genetic trade-off exists in using TESE sperm instead of ejaculated sperm: Higher aneuploidy rates (12% versus 6%)



Sperm retrieval procedure	IUI	IVF	ICSI
Vasal aspiration (MVSA, PVSA)	Maybe	Yes	Yes
Epididymal aspiration (MESA, PESA)	No	Yes	Yes
Testicular retrieval (TESA, TESE, microdissection TESE)	No	Yes	Yes

Comparisions

Vasal spermatozoa are more mature, motile and viable post thawing

Higher aneuploidy and lower DNA fragmentation rates in TESE/A vs ejaculated sperm

Microscopic techniques are more expensive, time consuming and require expertise

No head to head RCTs to recommend one technique over the other.’

SERTOLI CELL ONLY SYNDROME

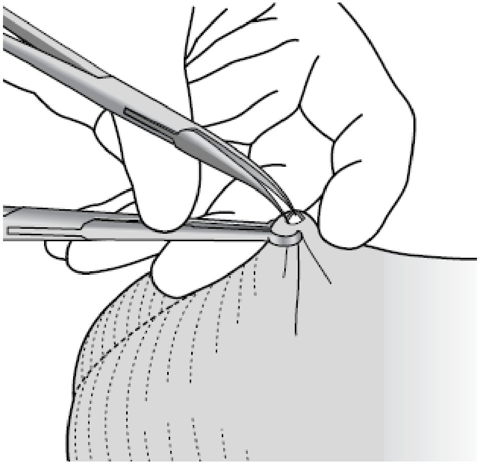
- Also known as germ cell aplasia
- Seminiferous tubules lined only by sertoli cells with absence of germinal epithelium
- Presentation is typically normal examination with normal volume ejaculate and azoospermia
- Clinical presentation similar to maturation arrest and hypospermatogenesis
- <10% of male infertility.
- Can be seen in Klinefelter’s
- Mostly idiopathic: Probable failure of germ cell migration
- AZFb, c mutations and Y microdeletions
- Apoptosis of germ cells due to expression of Fas and caspase 3
- Normal semen volume, azoospermia, normal testosterone, high (usual) FSH
- Semen pellet from centrifuging a specimen for 10 minutes at 1500-2000 rpm seen under 400X
- Testicular biopsy shows Sertoli cells only with absence/ small foci of germinal epithelium.
- Tubules may show small diameter with thickened basement membrane
- Microsurgical TESE with ICSI needed. Focal spermatozoa may be found in 20-40%
- Otherwise, donor sperm insemination/ adoption
- May be associated with a higher risk of testicular malignancy and warrants follow-up

NO SCALPEL VASECTOMY

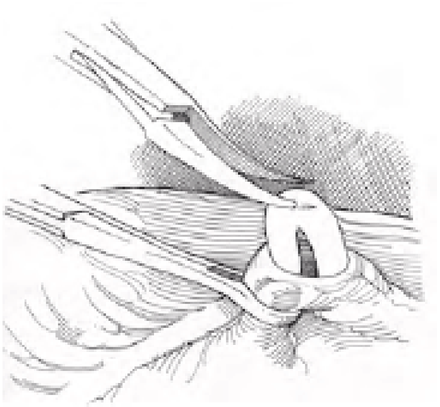
Li Quqiang 1974

- Warm room, shave on table, paint parts. No antibiotic
- Local anaesthesia: 1 or 2 % plain lignocaine or 50-50 lignocaine with bupivacaine
- Grasp vas through scrotum, scrotal wheal and inject into vasal sheath also
- The vas and perivasal tissue are firmly secured through the skin with a ring-tipped vas deferens fixation clamp

A modified, sharpened tipped curved hemostat is used to puncture the skin and the vas sheath, and the hemostat is spread to stretch the hole that is made.



The vas is pierced with one tip of the hemostat and lifted through the skin opening. The vas is regrasped with the ring clamp, and the hemostat is used to dissect the posterior perivasal tissue.



The vas deferens is divided, the occlusion technique of choice is employed, inspection is done for haemostasis and the vas deferens is replaced

Occlusion techniques: Low voltage intraluminal electrocautery, dartos interposition, metal clips, chemical occlusion.

Routine excision of a segment and submitting it for histopathology are not recommended by AUA.

80% of patients achieve azoospermia by 3 months and after 20 ejaculations. Check semen at 16 weeks. Persistent nonmotile sperm are present in 1.4% of patients after vasectomy.

If the semen analysis does not show azoospermia, periodic semen analyses can be obtained every 6 to 12 weeks until azoospermia.

Additional samples if the initial semen analysis has motile sperm or >100,000 non-motile sperm/mL.

Vasectomy should be repeated if any motile sperm are seen in the ejaculate 6 months after surgery

The Sperm- Check Vasectomy test is an immunodiagnostic procedure which may be performed at home. It is 96% accurate at predicting whether sperm counts were greater or less than a threshold of 250,000 sperm/ mL
Complications (0.5%) include haematoma, infection, scrotal sinus and post vasectomy pain

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ELECTROEJACULATION

For sperm retrieval in anejaculation (E.g. spinal injury, RPLND, DM, Multiple Sclerosis) or when penile vibrator has failed

***Mechanism of action*:**

- Direct electrical stimulation of seminal vesicles and terminal vas with a transrectal Seager electrode
- Direct pelvic sympathetic and somatic nerve stimulation causing ejaculation

Procedure

- Catheterize the patient in supine position and empty the bladder. .
- Betadine and Surgilube is to be avoided because of their spermicidal effect. Instead, the urethra is lubricated with glycerin or, preferably, by instillation of 2 cc of 6% simulated human tubal fluid and plasmanate.
- The pH of the urine assessed to ensure alkalinity (pH>6.5). Oral soda bicarb may be used
- Retrograde ejaculation occurs frequently in this procedure, an additional 10 cc of the simulated human tubal fluid and plasmanate is instilled into the bladder and pt is placed in lateral decubitus
- Digital rectal examination and anoscopy should be performed before and after the procedure to inspect the rectal ampulla and mucosa for any injury.
- Well lubricared probe into rectal ampulla, GA (discomfort) unless patient is asensate
- Alternating, progressive sine wave current: 5 volt for one second-pause-6 volt for one second-pause. Monitor vital parameters and rectal temp (should not exceed 40 C)
- Continue till ejaculation occurs. Usually does so between 5-10 Volt and 100-200 mAmp current
- The voltage at which the first erection/ejaculation occurs is noted and is then increased to a level 30% to 50% higher, depending on patient's tolerance and the rectal temperature which is constantly monitored and displayed. Ejaculation may be entirely retrograde.
- Sweating, piloerection on the things and buttocks, and erection may be the only signs that the patient is adequately stimulated and that ejaculation has occurred.
- If retrograde ejaculation present- Retrieval of sperm into cup with 3 cc of human tubal fluid (HTF).
- If lesion above T5, on guard against mass reflex- Discontinue, oral Nifedipine 20 mg, 15 min prior.

Outcomes

40% of the couples achieve pregnancy with IUI or IVF. Pregnancy rates are slightly better among couples in which the male partner had SCI (43%) or idiopathic anejaculation (33%) than retroperitoneal lymph node dissection (20%) or diabetes (0%).

RIGISCAN

-Assessment of erectile potential in the form of physiological erections during sleep

-Rigiscan (Timm Medical Technologies) is an automated, portable device used for NPTR, which combines the monitoring of radial rigidity, tumescence, number, and duration of erectile events.

-Two loops, one placed at the base of the penis and the other placed at the coronal sulcus
These loops record penile circumference and radial rigidity with timed, standardized constrictions

-A baseline initialization is performed with the patient in the office, and then it is calibrated for home use. At home,
-Registration of penile rigidity is done every 3 minutes and increased to every 30 seconds when the base loop detects a circumference increase of greater than 10 mm

Recommended criteria for normal NPTR include
four to five erectile episodes per night, mean duration longer than 30 minutes
an increase in circumference of more than 3 cm at the base and more than 2 cm at the tip,
maximal rigidity greater than 70% at both base and tip

-A computerized program has yields data measurements according to cumulative distribution of time + intensity measures, defined as tumescence activity units (TAU) and radial rigidity activity units (RAU)
-Potential limitations of Rigiscan include the fact that radial rigidity does not accurately predict axial rigidity and considerable variability apparently exists even in normal subjects
-The manner of testing does not allow verification of the presence of REM sleep which is correlated with nocturnal penile tumescence
-Erections during NPTR do not unequivocally equate with erections sufficient for sexual performance

-False-positive results are possible for various clinical situations (e.g., multiple sclerosis).
-False-negative results may occur in aging patients and in patients with depression or anxiety, which affect the physiology of sleep

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ICSI

Assisted reproduction technique where a single sperm is directly injected into the cytoplasm of a mature oocyte

Indications

- -Severe oligo/ azoospermia with or without astheno/ teratospermia (E.g. Klinefelter's, AZFc mutation, Sertoli only syndrome, maturation arrest, globospermia)
- -Prior failed IVF cycles
- -If genetic testing of embryo is needed pre-implantation
- -Fertilization of cryopreserved oocytes
- -Can be used in azoospermia with normal spermatozoa (E.g. CBAVD, b/l epididymal obstruction)
- -HIV discordant couples requiring assisted reproduction

Overall fertilization rates higher than IVF

Quality of sperm: Ejaculated>obstructive azoospermia>vasectomy (>10 yrs)>non-obstructive

Selection of spermatozoa

1. Motility:
    - -The embryo derives its centriolar apparatus and mitotic potential from the spermatozoa. The use of spermatozoa with a damaged or abnormal centriole could result in embryos with severe cleavage arrest.
    - -Motile sperms have normal centriolar apparatus.
    - -In case of poor motility, ensure viability of sperm by hypo-osmotic swelling/ Eosin-nigrosin staining test
2. Select spermatozoa with normal nuclear pattern on high magnification
3. Hyaluronic acid binding:
   -Competent mature sperm attach themselves to hyaluronic acid through specific receptors found on the sperm plasma membrane.
   -Selection of sperm bound to hyaluronic acid for ICSI facilitates selection of mature sperm with low levels of chromosomal aneuploidies and thus, lower rates of miscarriage

Procedure

-Performed by a trained embryologist
-Inverted microscope with high quality optics, warmer, micro-manipulators and injection systems set in a quiet part of the lab on an anti-vibration table
-Oocyte retrieval is performed: Controlled ovarian stimulation—transvaginal USG guided follicle aspiration/ cryopreserved oocytes are used
-Oocytes are denuded of cumulus-coronal cells using hyaluronidase and residual cells are gently aspirated with a finely pulled pipette.
-Only oocytes at metaphase II exhibiting a distinct extruded first polar body are used
-Pipette containing an immobilized spermatozoon is gently pushed through the zona pellucida and through the oolemma into the center of the oocyte.
-The spermatozoa should be delivered with the smallest possible amount of medium.
-Negative pressure is used to break the oolemma, followed by gentle aspiration of cytoplasm.
-Newer techniques: Laser assisted/ piezoelectric pipettes

Embryo transfer

-Pronuclear formation after ICSI distinguishes normally fertilized oocytes from abnormal.
-Normally, two pronuclei, male and female, and extruded 1st and 2nd polar bodies are seen.
-Abnormal zygotes should be discarded and normal ones may be cryopreserved.
-ICSI embryos have diminished implantation potential compared to IVF and four times the karyotype abnormalities compared to general population
-30% live birth rate

Outcomes

-Comparable growth and development of children born by ICSI
-Slight increase in chromosomal anomalies
-Y chromosome microdeletions (male embryo) and CFTR mutations are transferred to the embryo and parents should be counselled about this.
-The reproductive potential of women born by ICSI is unaffected but men seem to have low bulk semen parameters

Physiology of penile erection and pathophysiology of ED

Anatomy

Normal penis: 8.8 cm flaccid, 12.4 cm stretched and 12.9 cm erect

Corpora cavernosa : Two dorsal cylinders made of vascular sinusoids separated by smooth muscle bundles. Tunica albuginea (Outer longitudinal and inner circular with intracavernosal pillars radiating to the incomplete septum between the cylinders) surrounds the erectile tissue. Absent between 5 and 7 O' clock- weakest. Proximal ends (crura) diverge and attached to the inferior pubic rami.

Corpus spongiosum : Ventral, no outer layer or pillars, larger sinusoids. Low pressure during erections

Tunica: Elastic fibre lattice supporting collagen fibres (Type I>III) which are fewer.

Ligaments: Fundiform-Lateral and superficial to the albuginea. Suspensory: Arises from Buck's, one median and two lateral bundles surrounding the dorsal vein. Attaches albuginea to the symphysis

Arteries

Internal pudendal gives off perineal branch to become common penile which in turn, has 3 branches:

Dorsal (Glans engorgement)

Cavernosal (erections)

Bulbourethral. (urethra and spongiosum).

Dorsal and bulbourethral communicate via circumflex arteries and cavernosal gives off spiral helicine arteries into the erectile tissue of the cavernosa.

Classification of arterial supply (Droupy):

Type I: From internal pudendal

Type II: Both int pudendal and accessory (From obturator, vesical, external iliac or femoral)

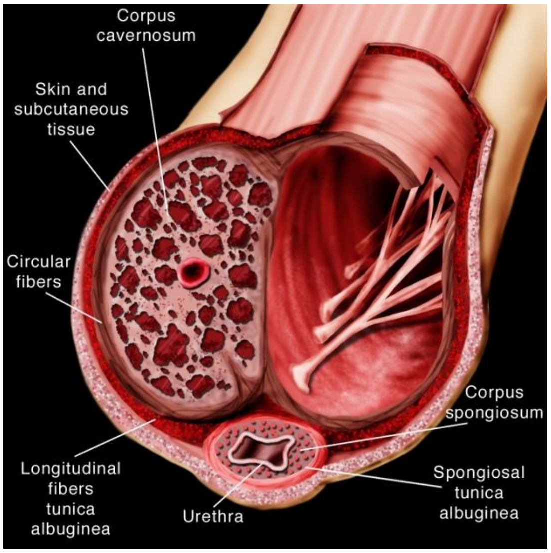
Type III: Exclusively accessory arterial supply

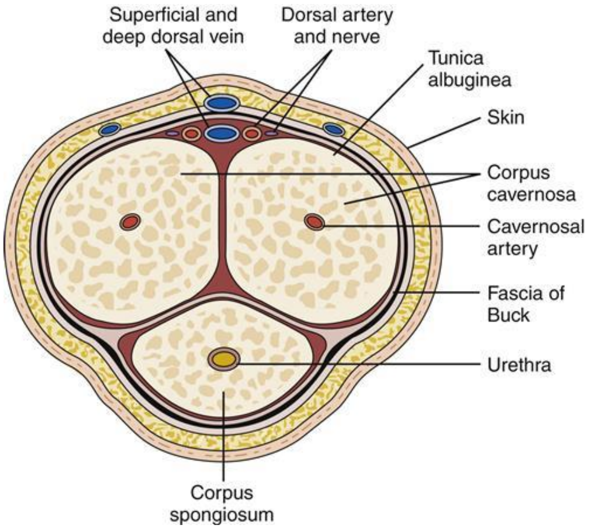
Veins

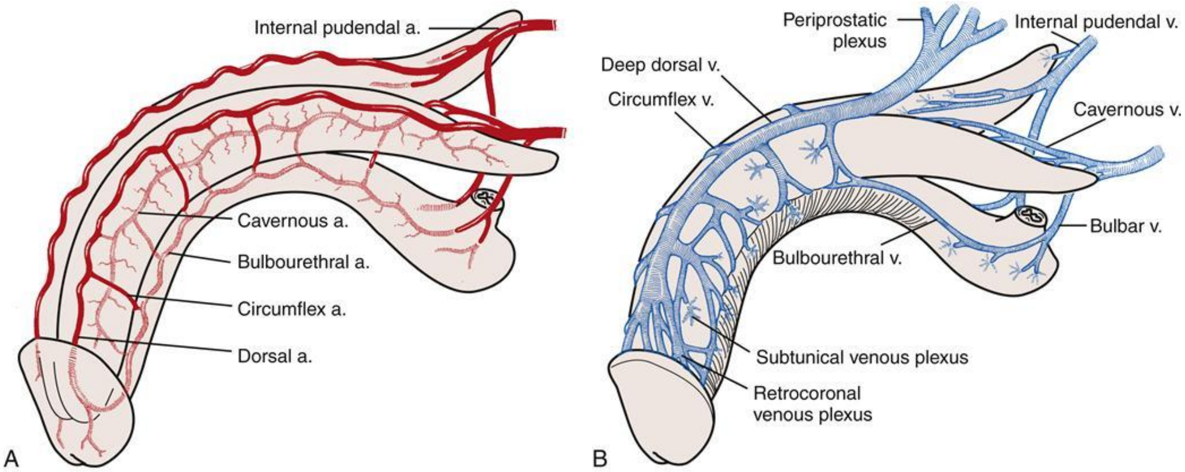
Subtuniceal venous plexus—emissary veins—deep dorsal vein (dorsal), circumflex (lateral) and periurethral veins (ventral).

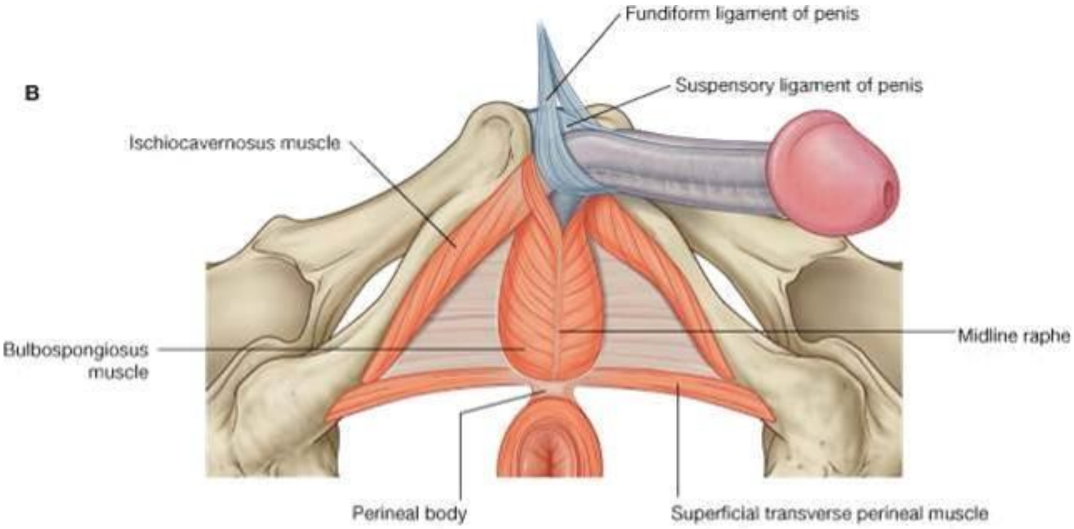
Glans and distal 2/3rd of cavernosa drain via deep dorsal vein. Deep dorsal vein joins periprostatic plexus

Proximal cavernosa: Cavernosal and periurethral veins—internal pudendal veins.


Corpus cavernosum
Skin and subcutaneous tissue
Circular fibers
Corpus spongiosum
Longitudinal fibers tunica albuginea
Urethra
Spongiosal tunica albuginea






B
Fundiform ligament of penis
Suspensory ligament of penis
Ischiocavernosus muscle
Bulbospongiosus muscle
Midline raphe
Perineal body
Superficial transverse perineal muscle

Steps in erection

Sexual stimulation triggers release of neurotransmitters from the cavernous nerve terminals. This results in relaxation of these smooth muscles and the following events:

Cavernosa

1. Dilatation of the arterioles and arteries by increased blood flow
2. Trapping of the incoming blood by the expanding sinusoids
3. Compression of subtunical venous plexuses between tunica and sinusoids
4. Stretching of the tunica occluding emissary veins between the inner circular and the outer longitudinal layers and further decreases the venous outflow
5. An increase in PO2 (to about 90 mm Hg from 35 mm Hg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (full-erection phase)
6. A further pressure increase (to several hundred millimeters of mercury) with contraction of the ischiocavernosus muscles (rigid-erection phase)

Spongiosum

-Compression of deep dorsal vein between Buck's fascia and tunica causes glanular tumescence
-Spongiosum and glans essentially function as a large arteriovenous shunt
-Rrigid erection phase, the ischiocavernosus forcefully compresses the spongiosal and penile veins causing further engorgement . However, pressures are 1/3rd those in the cavernosa

Detumescence

1. Transient corporeal pressure rise due to smooth muscle contraction against closed venous system.
2. Slow pressure decrease due to slow reopening of the venous channels & basal arterial flow.
3, Fast pressure decrease with fully restored venous outflow

Innervation

1. Somatic: Pudendal nerve (S2-4), sensory via free nerve endings (C + A delta) + corpuscular receptors
    S2-4: Onuf's nucleus
    Motor: Ischiocavernosus/ bulbospongiosus rhythmic contraction- ejaculation
2. Sympathetic: T10-12 (superior hypogastric plexus), ejaculation and detumescence
3. Parasympathetic: S2-4 (pelvic plexus), erection

Cavernous nerves: Sympathetic s from superior hypogastric + parasympathetics from pelvic plexus

Psychogenic erections: Preserved in lesions below T9 as sympathetic innervations is intact. The sympathetics are inhibited with visual/ erotic stimuli causing elongation and swelling but low rigidity

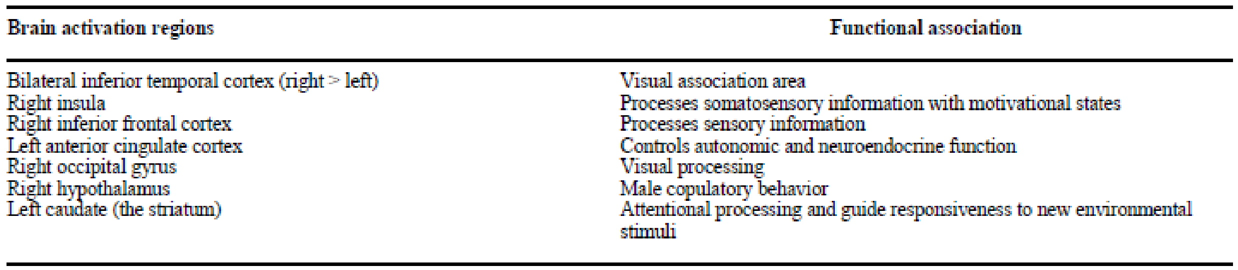
Ejaculation

Contraction of seminal vesicles/ prostate.
Rhythmic compression of bulbospongiosus expels ejaculate once external sphincter relaxes
Contraction of bladder neck prevents retrograde ejaculation.

Supraspinal pathways

-Hypothalamic medial preoptic area (MPOA) and the paraventricular nucleus (PVN) of the hypothalamus and hippocampus are integration centers for sexual function and erection
-Electrostimulation of this area induces erection
-Stimulation of the dorsal nerve of the influences the activity of 80% of the neurons in the MPOA.
-Efferent pathways from the MPOA enter midbrain near substantia nigra- lesions here (E.g. Parkinson's) cause ED.
-Direct projection from hypothalamic nuclei to the lumbosacral autonomic erection centers
-Projections from the nucleus paragigantocellularis: Inhibitory serotonergic innervation, demonstrated in hypothalamus & the limbic system

Brain centres



Brain activation regions	Functional association
Bilateral inferior temporal cortex (right > left)	Visual association area
Right insula	Processes somatosensory information with motivational states
Right inferior frontal cortex	Processes sensory information
Left anterior cingulate cortex	Controls autonomic and neuroendocrine function
Right occipital gyrus	Visual processing
Right hypothalamus	Male copulatory behavior
Left caudate (the striatum)	Attentional processing and guide responsiveness to new environmental stimuli

-Nocturnal erection occurs mostly during rapid-eye-movement (REM) sleep. PET scanning shows increased activity in the pons, amygdala and the anterior cingulate gyrus but decreased activity in the prefrontal and parietal cortex.
-The left gyrus rectus, a portion of the medial orbitofrontal cortex remained activated in men with hypoactive sexual disorder, while it remained deactivation in healthy men in response to visual stimuli
-In men with psychogenic ED extended activation of cingulate gyrus and frontal basal cortex was seen
-Right> left hemisphere activation is a common finding with sexually stimuli.

Molecular mechanism of smooth muscle contraction

Noradrenaline: Alpha receptors—decreased cAMP
Endothelin/PGF2 alpha: PIP2 cleaved to IP3 (Ca channels opened on cell membrane and endoplasmic reticulum) and DAG (Activates Protein Kinase C)
Increased Ca binds to Calmodulin and activates Myosin light chain kinase
MLCK phosphorylates myosin light chain and causes formation of myosin cross bridges--contraction

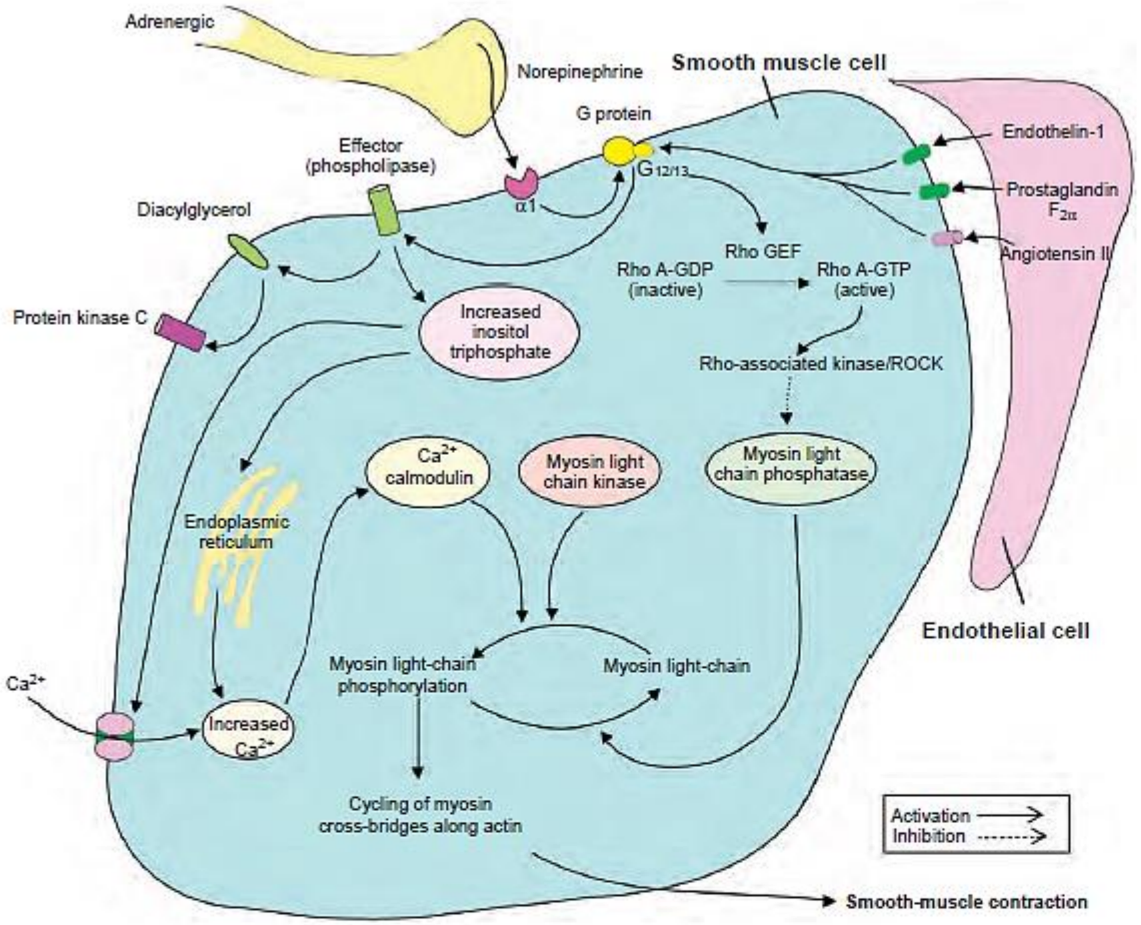


Figure 26-9. **Molecular mechanism of penile smooth muscle contraction. Norepinephrine from sympathetic nerve endings and endothelins, angiotensin II, and prostaglandin $F_{2\alpha}$ from the endothelium activate receptors on smooth muscle cells to initiate the cascade of reactions that eventually result in elevation of intracellular calcium concentrations, activation of Rho-kinase, and smooth muscle contraction. Protein kinase C is a regulatory component of the Ca^{2+}-independent, sustained phase of agonist-induced contractile responses. GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GTP, guanosine triphosphate.**

Smooth muscle relaxation

NO and PGE2 activate adenylyl/ Guanylyl cyclase
cAMP and cGMP are produced which open K channels and cause Ca to return to endoplasmic reticulum
This relaxes muscle
PDE5 inhibitors block degradation of cGMP to 5’ GMP thereby prolonging smooth muscle relaxation

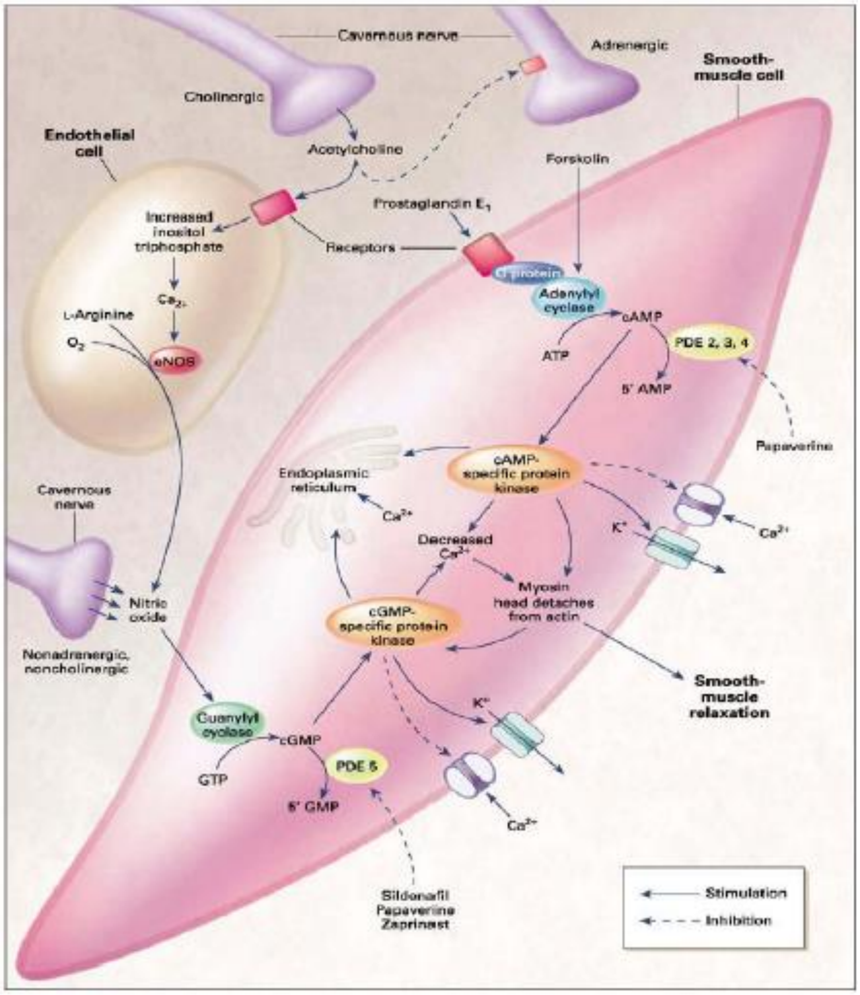


Figure 3.
Molecular mechanism of penile smooth muscle relaxation. The intracellular second messengers mediating smooth muscle relaxation, cAMP and cGMP, activate their specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium leads to smooth muscle relaxation. Sildenafil inhibits the action of PDE5 and thus increases the intracellular concentration of cGMP. Papaverine is a nonspecific phosphodiesterase inhibitor. eNOS, endothelial nitric oxide

ED pathophysiology

Classification:

- Vasculogenic: Arterial, venous. Mixed (DM, HTN, dyslipidaemia, obesity, smoking, PFUI)
- Neurogenic : Central (stroke, tumour, Parkinson's), peripheral (DM, pelvic Sx, CKD)
- Anatomical : Hypo/ epispadias, micropenis, Peyronie's, penile cancer, phimosis
- Endocrinological: Hypogonadism, hyper/ hypo thyroidism or cortisolism, prolactin excess
- Drug induced: Thiazides, SSRI, TCA, neuroleptics, antiandrogens, alcohol. Cocaine, marijuana
- Psychogenic: Generalized lack of arousability or disorder of intimacy
    - Situational: Partner related, performance anxiety/ PE, depression

Psychogenic

-Most common- 90%
-Direct inhibition of the spinal erection center by the brain or excessive sympathetic outflow causing smooth muscle contraction

Neurogenic

-20%
-MPOA and PV nuclei of hypothalamus, basal frontal/ temporal cortex may be affected by Parkinson's, MSA, MS, tumours, stroke- ED
-Lesions above T9-No psychogenic erections
-RP/ radical pelvic surgery/ trauma- Dorsal nerve injury and ED. Incidence after RP is 25-90%, less with nerve sparing approaches especially if the patient has good erectile function pre-op. Erections better preserved with PDE5i: Nerve stimulation, maintenance of cavernosal erectile tissue
-Recovery of erections after RP may take 6-24 months.

Endocrinological

-Testosterone: Libido, nocturnal erections, frequency of intercourse, penile arterial supply, NOS activity
Maintains cavernosal smooth muscle and sinusoids
-Thyroid/ cortisol/ prolactin disorders: Low testosterone and libido

Arteriogenic

-Reduced arterial flow into sinusoids-reduced blood volume and O2
-Diminished O2- Damage to smooth muscle, reduced muscle and increased collagen/ decreased elastin
-Fibrosis causes loss of contact between smooth muscle cells and loss of coordinated muscle activity
-Increased collagen and decreased Elastin reduces compliance of sinusoids
-PGE1 suppresses collagen synthesis via TGFβ1. Intracavernous injection of PGE1 may prevent intracavernosal fibrosis.
-Enhanced tone of blood vessels causing vasoconstriction
-Impairment of endothelium-dependent relaxation in response to Acetylcholine/ stretch: Angiotensin II, thromboxane and superoxide

Veno-occlusive disease

1. Degenerative changes in subtunical areolar layer(Peyronie's disease, old age, and diabetes) or injury to the tunica albuginea (penile fracture: Iinadequate compression of the subtunical + emissary veins.
2. Alterations in the fibroelastic components of the trabeculae, cavernous smooth muscle, and endothelium may result in venous leak.
3. Insufficient trabecular smooth muscle relaxation, causing inadequate sinusoidal expansion and insufficient compression of the subtunical venules, may occur in an anxious individual with excessive adrenergic tone
4. Acquired venous shunts after operative correction of priapism

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Management of ED

Medical conditions associated with ED

Vasculogenic : Arterial, venous. Mixed (DM, HTN, dyslipidaemia, obesity, smoking, PFUI)

Neurogenic : Central (stroke, tumour, Parkinson's), peripheral (DM, pelvic Sx, CKD)

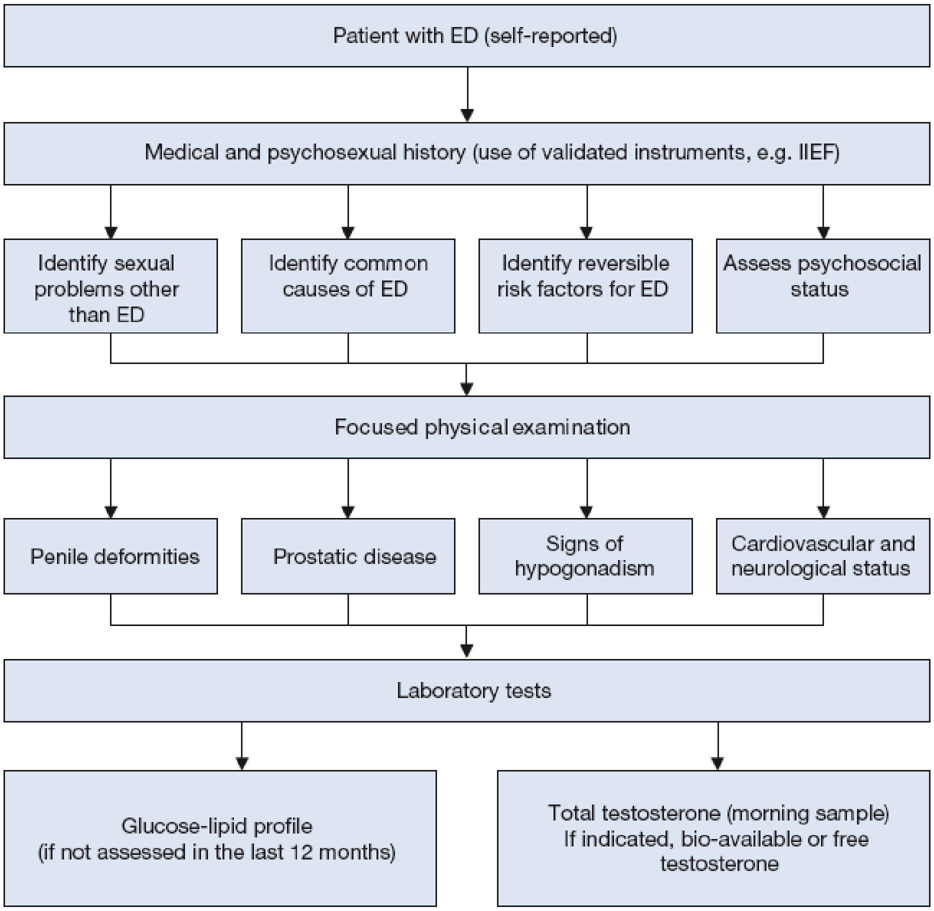
Anatomical : Hypo/ epispadias, micropenis, Peyronie's, penile cancer, phimosis

Endocrinologic: Hypogonadism, hyper/ hypo thyroidism or cortisolism, prolactin excess

Drug induced : Thiazides, SSRI, TCA, neuroleptics, antiandrogens, alcohol. Cocaine, marijuana

Psychogenic : Generalized lack of arousability or disorder of intimacy
Situational: Partner related, performance anxiety/ PE, depression

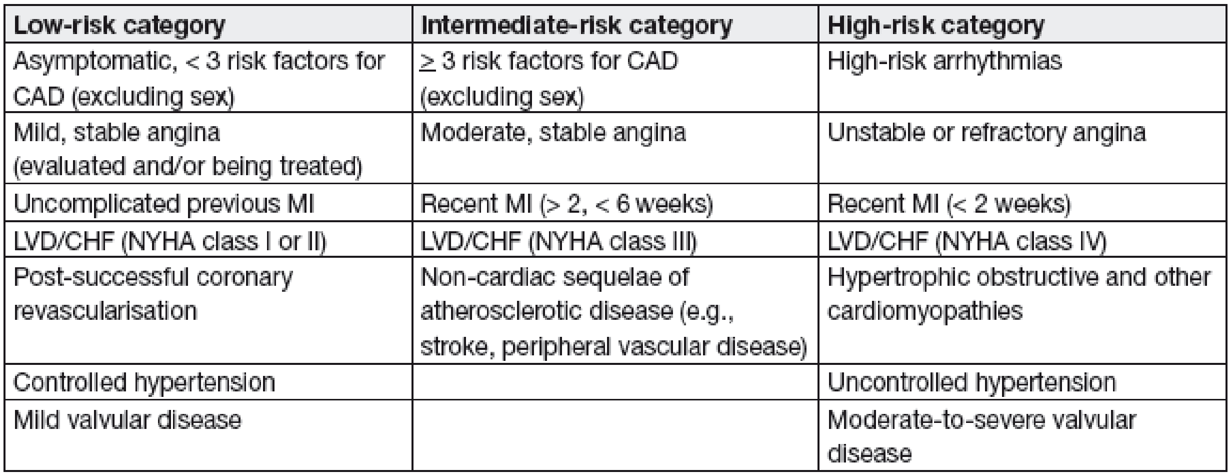
Basic workup


Patient with ED (self-reported)
Medical and psychosexual history (use of validated instruments, e.g. IIEF)
Identify sexual problems other than ED
Identify common causes of ED
Identify reversible risk factors for ED
Assess psychosocial status
Focused physical examination
Penile deformities
Prostatic disease
Signs of hypogonadism
Cardiovascular and neurological status
Laboratory tests
Glucose-lipid profile (if not assessed in the last 12 months)
Total testosterone (morning sample) If indicated, bio-available or free testosterone

Other bloods: FSH, LH, TSH, cortisol (late night)

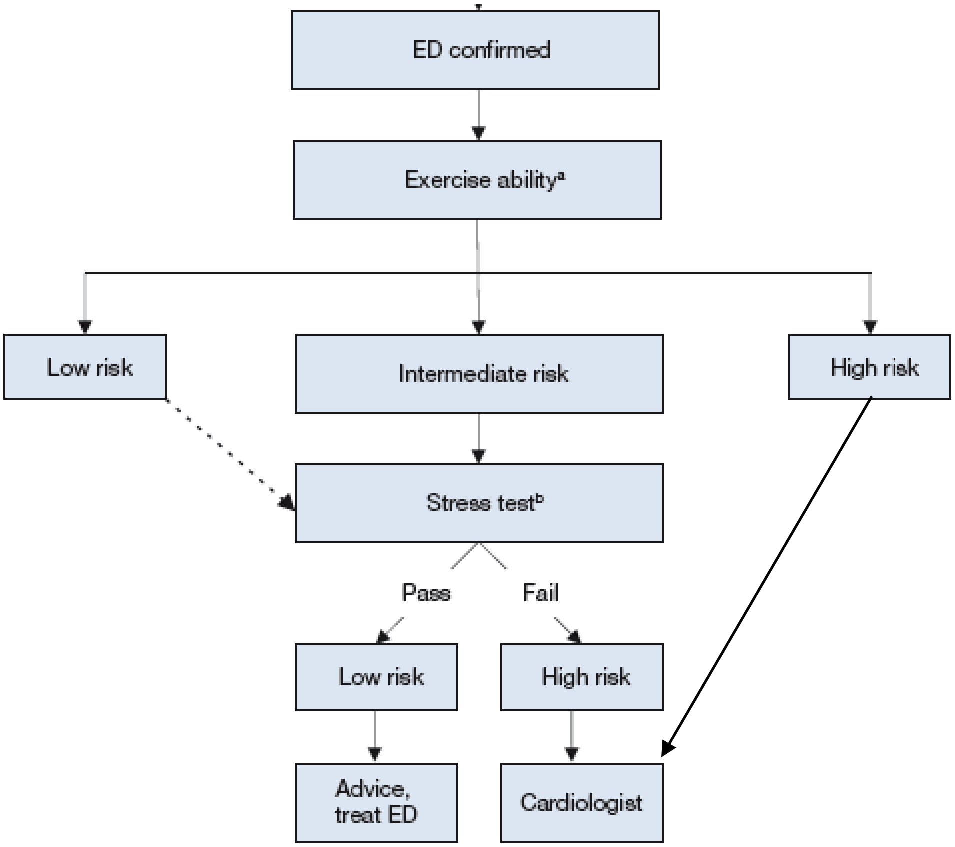
Cardiac risk assessment

High association between ED and cardiovascular/ cerebrovascular diease
ED is a marker of generalized vascular disease
Risk stratification according to Princeton consensus



Low-risk category	**Intermediate-risk category**	**High-risk category**
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

Management algorithm based on cardiac risk



Additional special tests

Nocturnal penile tumescence (Rigiscan): 4-5 episodes, each 30 min, 3 cm at base and 2 cm at apex and rigidity >70% at base and tip=normal
PIPE: Vascular integrity assessed. A positive test is a rigid erectile response (unable to bend the penis) that appears within ten minutes after the intracavernous injection and lasts for 30 minutes. Duplex more accurate

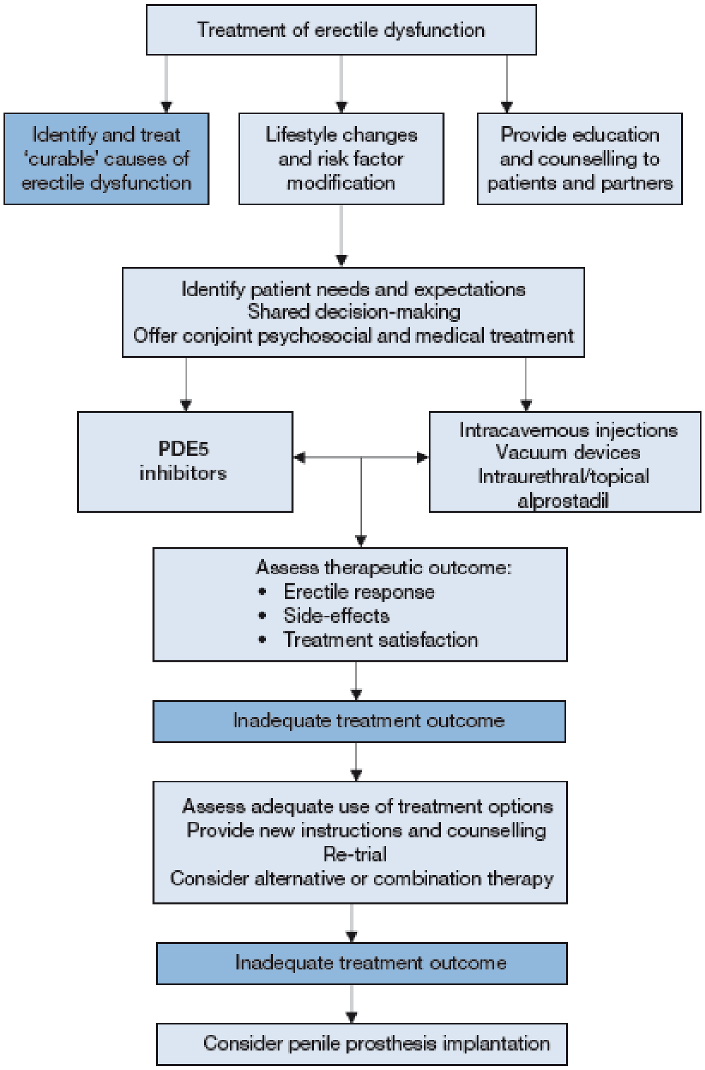
Duplex USG: Done after intracavernosal injection of Papaverine. >30 cm/sec peak systolic, <3 cm/ sec end diastolic and RI >0.8=Normal.

Arteriography and dynamic infusion cavernosometry or cavernosography: Pre revascularization

Nerve conduction velocity and Bulbocavernosus reflex latency

Consultations
Psychiatry, Endocrinology, Cardiology

Treatment algorithm


Treatment of erectile dysfunction
Identify and treat 'curable' causes of erectile dysfunction
Lifestyle changes and risk factor modification
Provide education and counselling to patients and partners
Identify patient needs and expectations
Shared decision-making
Offer conjoint psychosocial and medical treatment
PDE5 inhibitors
Intracavernous injections
Vacuum devices
Intraurethral/topical alprostadil
Assess therapeutic outcome:
• Erectile response
• Side-effects
• Treatment satisfaction
Inadequate treatment outcome
Assess adequate use of treatment options
Provide new instructions and counselling
Re-trial
Consider alternative or combination therapy
Inadequate treatment outcome
Consider penile prosthesis implantation

Oral PDE5i-1st line
Intracavernosal/ urethra/ vacuum: 2nd line

PDE5i

-Enhance recovery post RP if given peri-op: ? Nerve stimulation/ maintenance of cavernosal architecture
-Only if nerve sparing approach
-Tadalafil most effective. Usual response rates 70%
-Other intracavernosal modalities may also be used before implant+/- sphincter or sling
-Daily use of Tadalafil 5 mg also efficacious and improves QoL

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Dose	25,50,100 mg	5, 10, 20 mg	5, 10, 20 mg	50, 100, 200 mg
Onset of action	30-60 min	30 min	30 min	15-30 min
T1/2 (hrs)	3	17.5	4	6-17
Lasts up to(hrs)	12	36	12	24
Fatty meal	Delays action	No interaction	Delays action	Delays action
Alpha blocker	Tamsulosin	All	Tamsulosin	Tamsulosin
Gap before nitrate administration (hrs)	24	48	24	24
Specific	-Most efficacious -Vision disturbed (cyanopsia)	-Most tolerable -LUTS+ED -Myalgia	-Vision disturbed (cyanopsia- blue tinted vision)	-Most selective -No hepatic/ renal dosing

General side effects: GI, palpitations, flushing, headache, nasal congestion, dizziness (hypotension)

Contraindications:
i) Myocardial infarction, stroke, or life-threatening arrhythmia in the last six months
ii) Resting hypotension (blood pressure < 90/50 mmHg) or hypertension (> 170/100 mmHg)
iii) Unstable angina, angin, congestive heart failure NYHA Class IV
iv)Requiring nitrates

Non responders
-Check dose (Inadequate) and time given for drug before intercourse (Too long/ short)
-Administration with meals or CYP3A4 inducers like Carbamazepine
-Substitute with another PDE5i
-Second line therapy

Vacuum device
-Alone/ with PDE5i/ injections
-Elderly men with infrequent intercourse who have comorbid illnesses precluding drug therapy
-In cavernosal fibrosis after priapism before penile implantation (10 min, twice daily)
-Types: Manual with pump and cylinder, pump and cylinder separate or automatic
-Along with onstriction ring at root of penis, cause engorgement enough for penetration
-Pain, numbness, inability to ejaculate, oedema, petechiae
-Not to be used in those on anticoagulants- Bruising
-Remove within half an hour of intercourse to avoid ischaemia and necrosis

Intracavernosal injection therapy

-Alprostadil (Caverject/ Edex)- 5-40 ug per dose (PGE1)
-Papaverine-20-80 mg, usually in combination. Non specific PDE inhibitor used usually in combination
-Bimix: Papaverine+chlorpromazine
-Trimix: Papaverine+chlorpromazine+Alprostadil
-Invicorp: VIP+phentolamine
- An office-training programme is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners.
-0.1-0.2 ml into one corpus, stroke and fantasize, repeat if inadequate at 30 min
-The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture
-Efficacy 70%, satisfaction 90%
-Pain (50%), fibrosis (2%), priapism (1%)
-Lignocaine and 30 G needle: Less pain
-50% dropout usually in first 3 months: Lack of efficacy, want permanent solution, fear needles, complications, lack of spontaneity

Intraurethral Alprostadil

-Alprostadil (125-1000 µg) in a medicated pellet (MUSE™)
-30-70% effective. Pain, burning and dizziness
-May be given topically as well (200-300 ug) as a cream applied through the meatus

Penile prosthesis (May be expanded from the short note)

-Semi-rigid/ inflatable (2/3 piece)
-Inflatable: Best erection as well as tumescence, costly, mechanical failure (5% in 5 yrs)
-Penoscrotal or suprapubic approach
-Infections (2-3%): Explant and delayed reimplant or antibiotic wash followed by immediate reimplant (80% salvage)

Biochemical diagnosis of phaeochromocytoma and perioperative management of phaeochromocytoma

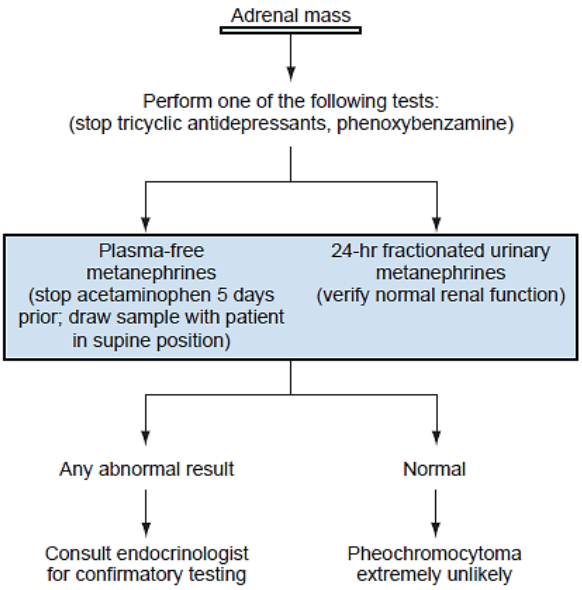
Biochemical diagnosis:

Phaeochromocytoma produce catecholamines (dopamine, norepinephrine and epinephrine) and the detection of catecholamines and their metabolites in urine and plasma aid in the diagnosis.

Catecholamines and their metabolites, including metanephrines, are conjugated with a sulfate moiety in the bloodstream. The term *free* refers to compounds that are not conjugated and lack this sulfate group. In the past, assays that measured "total"amounts of catecholamine metabolites were used. These assays were not able to discriminate between "free" and "sulfonated" compounds and were largely inferior in their test characteristics compared with current methods. Moreover, in the past, assays did not always distinguish compound subtypes and reported the aggregate level of catecholamines or metanephrines.

The term *fractionated* is used when the laboratory report details not only the amount of each compound type (e.g., metanephrines), but also the relative concentrations of each compound (eg: normetanephrine and metanephrine).

Because this conversion of catecholamines to metanephrines is an **uninterrupted** process within pheochromocytomas, measurement of plasma concentration of metanephrines is a much more sensitive means of tumor detection than the measurement of rises in plasma catecholamines**, which may be paroxysmal**. The measurement of metanephrine levels in plasma or urine represents the foundation for pheochromocytoma diagnosis and is extremely sensitive. The 2005 International symposium on Pheochromocytoma concluded that one of these two tests should be used for initial diagnosis and screening for pheochromocytoma.


Adrenal mass
Perform one of the following tests:
(stop tricyclic antidepressants, phenoxybenzamine)
Plasma-free metanephrines (stop acetaminophen 5 days prior; draw sample with patient in supine position)
24-hr fractionated urinary metanephrines (verify normal renal function)
Any abnormal result
Normal
Consult endocrinologist for confirmatory testing
Pheochromocytoma extremely unlikely

Testing algorithm to evaluate adrenal mass for catecholamine secretion.

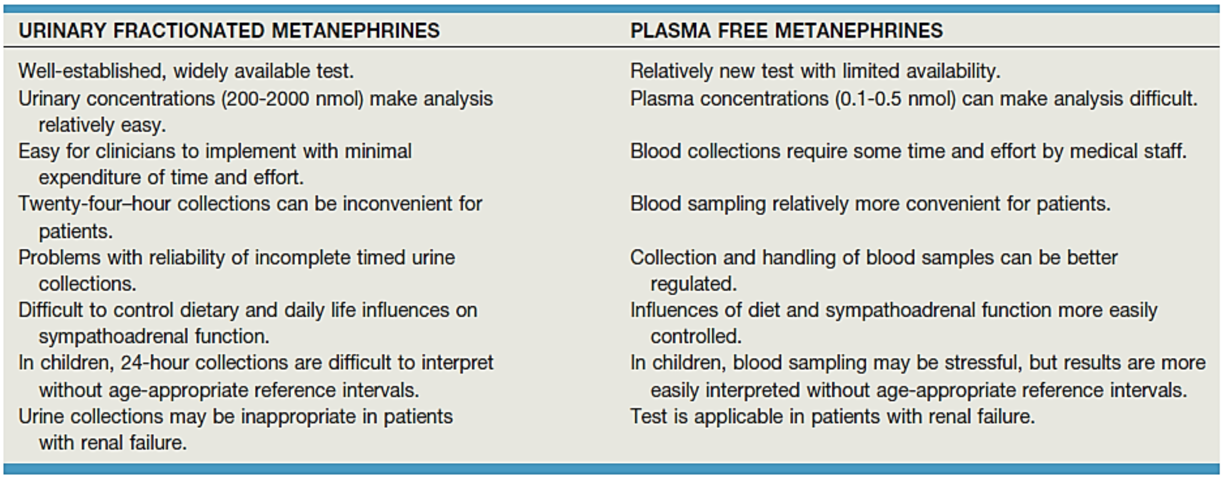
Plasma free metanephrines:
The measurement of plasma free (fractionated) metanephrines has gained popularity owing to ease of testing and excellent test characteristics. The sensitivity was 99% in cases of sporadic and 97% in familial pheochromocytoma. Specificity was reported to be 82% for sporadic and 96% for familial cases.

- Ideally, patients should not consume food or liquids after midnight before the study. Caffeinated beverages must be avoided especially. Acetaminophen can produce a false-positive result owing to cross reactivity in the assay and should be stopped for at least 5 days before testing.
- Tricyclic antidepressants and phenoxybenzamine should also be stopped, because these have been shown to be responsible for falsepositive results. Usual antihypertensive therapy can be continued. Although β-blockade can potentially result in a false-positive test result, the current recommendation is to stop the medication only on repeat testing. Ideally, the serum sample should be drawn with the patient in the supine position after at least 20 minutes of supine rest. Position is especially important if a positive result has been obtained and confirmatory testing is being performed.

24 hour urinary fractionated metanephrines:

- As in all 24-hour urine collections, the patient is instructed to discard the morning's first voided urine and begin to collect all subsequent voided samples. The last sample that is collected is the first morning's void of the following day.
- Creatinine levels in the collection must be checked to verify completeness of the collection. The test is most accurate in patients with normal renal function. Tricyclic antidepressants and phenoxybenzamine should be stopped.
- Sensitivity is around 97% with a specificity of 91%.

The pros and cons of the two tests are as follows:



URINARY FRACTIONATED METANEPHRINES	PLASMA FREE METANEPHRINES
Well-established, widely available test.	Relatively new test with limited availability.
Urinary concentrations (200-2000 nmol) make analysis relatively easy.	Plasma concentrations (0.1-0.5 nmol) can make analysis difficult.
Easy for clinicians to implement with minimal expenditure of time and effort.	Blood collections require some time and effort by medical staff.
Twenty-four–hour collections can be inconvenient for patients.	Blood sampling relatively more convenient for patients.
Problems with reliability of incomplete timed urine collections.	Collection and handling of blood samples can be better regulated.
Difficult to control dietary and daily life influences on sympathoadrenal function.	Influences of diet and sympathoadrenal function more easily controlled.
In children, 24-hour collections are difficult to interpret without age-appropriate reference intervals.	In children, blood sampling may be stressful, but results are more easily interpreted without age-appropriate reference intervals.
Urine collections may be inappropriate in patients with renal failure.	Test is applicable in patients with renal failure.

The other biochemical tests for evaluation of phaeochromocytoma that are not frequently used are:

a) Vanilyllmandelic Acid resting (**VMA**) – VMA is the primary end product of all catecholamine metabolisms in the body hence not specific to adrenal gland. Therefore the relative rise of VMA levels in the presence of a pheochromocytoma is much less dramatic than the rise seen in the levels of metanephrines, and the **sensitivity** of urine VMA levels is therefore low (**below 65%** in some series). However, the **specificity** of the test is high, especially in nonfamilial cases (**99%**).

b) Clonidine suppression testing – Clonidine an alpha 2 agonist suppresses catecholamine production (specifically norepinephrine) from the sympathetic nervous system with no effect on phaeochromocytoma. This test may be used as secondary testing in borderline cases. Clonidine can cause significant hypotension and has to be used with caution.

c) Chromogranin A testing – This test again has low sensitivity (around 85%) but may be used as secondary testing in borderline cases. Chromogranin is cleared by renal route, so may not be accurate in renal dysfunction.Perioperative management of phaeochromocyotma:

Preoperative management

Catecholamines exert their action through alpha-1 mediated vasoconstriction and beta-1 mediated inotropy and tachycardia to cause hypertension. Additionally the vasoconstriction causes a state of intravascular volume contraction.

These hemodynamic alterations make the perioperative management of phaeochromocytoma challenging.

All patients with abnormal metabolic work up and hypertensive need preop sympathetic blockade to control the hypertension before the time of surgery. The role of sympathetic blockade in a normotensive asymptomatic patient is one of debate especially in light of newer compelling data. However, most centres still routinely go ahead with preoperative sympathetic blockade.

1) **Alpha blockade**: Alpha blockade is started 7-14 days before surgery. Phenoxybenzamine (non selective, irreversible alpha blocker) has been the most studied drug for alpha blockade. It is started at a dose of 10mg BD and escalated gradually upto a dose of 1mg/kg (Paediatric dose 0.2 mg/kg). The side effects of phenoxybenzamine include orthostatic hypotension, tachycardia, nausea, abdominal pain and headache and drowsiness (due to crossing of blood brain barrier).
   Alpha blockade may also be accomplished with alpha-1 selective drugs such as terazosin, doxazosin or prazosin.
2) **Beta-blockade**: Beta blockade is used if there is arrhythmias/reflex tachycardia with alpha blockade. However alpaha blockade should always precede beta blockade to prevent unopposed action of epinephrine on alpha-1 on the vessels that now lack beta-2 mediated dilation. Also, the inhibition of beta-1 mediated cardiac drive before arteriolar dilation may lead to acute cardiac insufficiency and pulmonary edema.
   Again for beta blockade beta-1 selective drugs like atenolol and metaprolol are preferred even though propranolol was the drug traditionally used.
3) **Catecholamine synthesis blockade** –Metyrosine which is an inhibitor of tyrosine hydroxylase inhibits catecholamine synthesis. This drug is used in conjunction with alpha blocade depending on institutional practices. The drug causes extrapyramidal side effects and takes 2-3 days to have full effect.
4) **Calcium channel blockers** – CCBs like nicardapine may be used preoperatively to control hypertension either as adjunct or in refractory cases. It avoids the reflex tachycardia and postural hypotension seen with alpha blockade.
5) **Intravascular volume management:** One of the most important components of preop management. Salt and fluid intake to be increased once catecholamine blockade initiated. Patient encouraged taking at least 2-3 litres/day with 5-10g salt/day. Serial hematocrit fall of 5-10% may be a surrogate for adequate hydration. Two days before surgery the patient is to be admitted and intravenous fluid hydration initiated. Alpha blockade to be withheld on the morning of surgery.
6) Insulin may be administered if there is alpha two induced hyperglycemia.
7) Cardiac evaluation – Complete preoperative cardiac evaluation including ECHO to be done to ensure cardiac fitness before surgery.
8) **Adequacy/goals of alpha blockade (Roizen criteria modified**) –
   a. Adequate BP control for atleast 3-5 days preoperatively
   b. Systolic BP <130mmHg Diastolic <80mmHg
   c. Heart rate <80/min
   d. Orthostatic hypotension >80/45 mmHg
   e. Ventricular arrhythmia < 1 in 5 minutes
   f. No ST/T changes on ECG
   g. Hematocrit <45

Intraoperative management

In view of challenging hemodynamic changes senior, experienced anaesthetist should handle the case. There should be intensive monitoring equipments and facility in the place. Anaesthetic drugs that precipitate catecholamine secretion should be avoided.

Invasive BP monitoring with arterial line is needed. Also a central line/pulmonary line for volume status assessment should be in place. Inhaled anaesthetics with least cardiac effects should be used.

For intraoperative BP fluctuations before the tumor is out – GTN/nitroprusside/nicardapine/phentolamine may be used for rapid BP control while esmolol and lidocaine may be used for arrhythmias.

Once the tumor is removed, fall in BP should be managed with IVFs and alpha agonists.

Postoperative management

Immediate post op ICU care may be required till hemodynamic stability is attained. Rebound hypoglycaemia may occur and close glycemic monitoring is required in the first 24-48 hours.

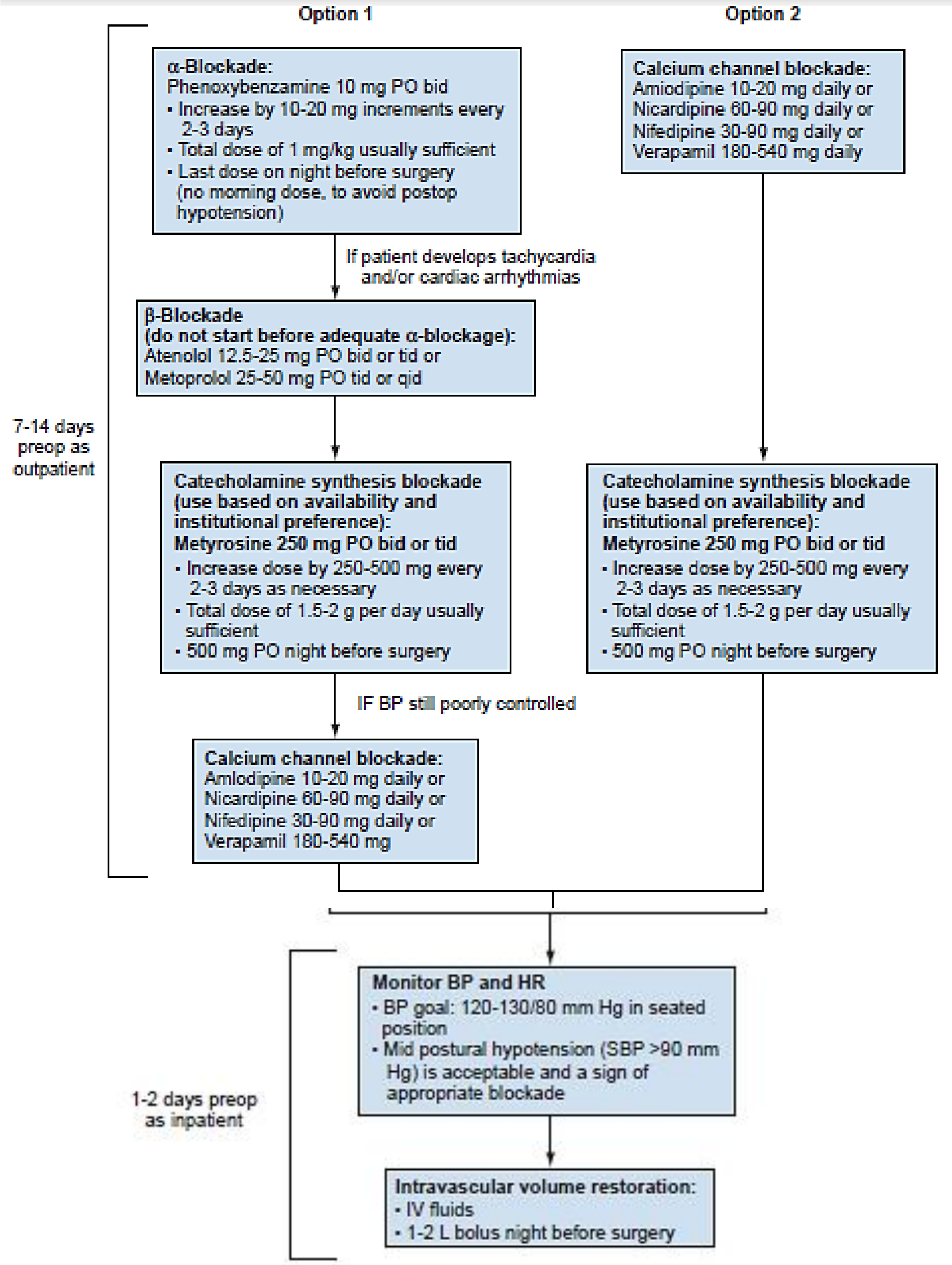

Option 1
Option 2
α-Blockade:
Phenoxybenzamine 10 mg PO bid
• Increase by 10-20 mg increments every 2-3 days
• Total dose of 1 mg/kg usually sufficient
• Last dose on night before surgery (no morning dose, to avoid postop hypotension)
Calcium channel blockade:
Amiodipine 10-20 mg daily or
Nicardipine 60-90 mg daily or
Nifedipine 30-90 mg daily or
Verapamil 180-540 mg daily
If patient develops tachycardia and/or cardiac arrhythmias
β-Blockade
(do not start before adequate α-blockage):
Atenolol 12.5-25 mg PO bid or tid or
Metoprolol 25-50 mg PO tid or qid
7-14 days preop as outpatient
Catecholamine synthesis blockade (use based on availability and institutional preference):
Metyrosine 250 mg PO bid or tid
• Increase dose by 250-500 mg every 2-3 days as necessary
• Total dose of 1.5-2 g per day usually sufficient
• 500 mg PO night before surgery
Catecholamine synthesis blockade (use based on availability and institutional preference):
Metyrosine 250 mg PO bid or tid
• Increase dose by 250-500 mg every 2-3 days as necessary
• Total dose of 1.5-2 g per day usually sufficient
• 500 mg PO night before surgery
IF BP still poorly controlled
Calcium channel blockade:
Amlodipine 10-20 mg daily or
Nicardipine 60-90 mg daily or
Nifedipine 30-90 mg daily or
Verapamil 180-540 mg
Monitor BP and HR
• BP goal: 120-130/80 mm Hg in seated position
• Mild postural hypotension (SBP >90 mm Hg) is acceptable and a sign of appropriate blockade
1-2 days preop as inpatient
Intravascular volume restoration:
• IV fluids
• 1-2 L bolus night before surgery

Figure 65-20. **Preoperative medical management in patients with pheochromocytoma. BP, blood pressure; HR, heart rate; IV, intravenous; PO, by mouth; SBP, systolic blood pressure. (Modified from Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069–79.)**

Incidentaloma

Adrenal incidentalomas are **unsuspected adrenal masses greater than 1 cm in diameter** identified on cross-sectional imaging performed for **seemingly unrelated causes**.
The frequency of adrenal incidentalomas is relatively high, with contemporary imaging series reporting an incidence **of approximately 5%,** similar to that found in historical autopsy data. The incidence of the incidental adrenal mass increases with age, with a risk of less than 0.5% in individuals in their 20s and up to 7% in those 70 years of age or older.

About 20% of incidentalomas are potential surgical lesion as follows:

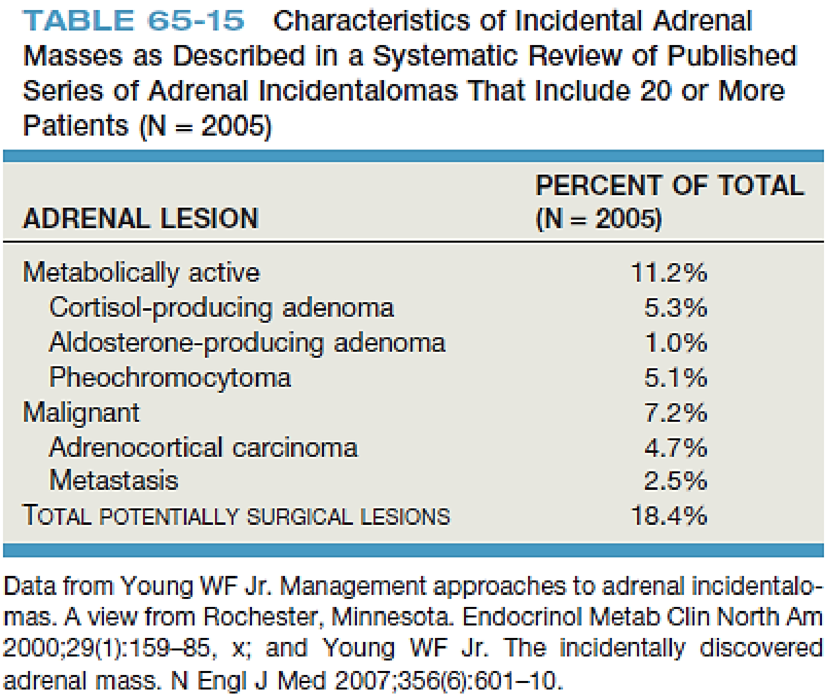


TABLE 65-15 Characteristics of Incidental Adrenal Masses as Described in a Systematic Review of Published Series of Adrenal Incidentalomas That Include 20 or More Patients (N = 2005)

ADRENAL LESION	PERCENT OF TOTAL (N = 2005)
Metabolically active	11.2%
Cortisol-producing adenoma	5.3%
Aldosterone-producing adenoma	1.0%
Pheochromocytoma	5.1%
Malignant	7.2%
Adrenocortical carcinoma	4.7%
Metastasis	2.5%
TOTAL POTENTIALLY SURGICAL LESIONS	18.4%

Data from Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am 2000;29(1):159–85, x; and Young WF Jr. The incidentally discovered adrenal mass. N Engl J Med 2007;356(6):601–10.

Imaging modalities:

The imaging modality of choice for evaluation is CT scan – non contrast, arterial phase (1 min after contrast injection) and delayed phases (15 min after contrast).

70% of benign adenomas are lipid rich with characteristic attenuation of less than 10 Hus which can be identified on non contrast phase. The 30% atypical cases though lipid poor still show similar washout characteristics (rapid washout) on contrast and delayed images.

Absolute percent of washout more than 60% and relative percent washout of >40% has almost perfect sensitivity and specificity for diagnosis of adenoma.
MRI with chemical shift may also be used for this purpose. A loss of signal in the out of phase image is suggestive of benign adenoma. However CT scan is superior to MRI even with gadolinium contrast for diagnosis of adenoma.

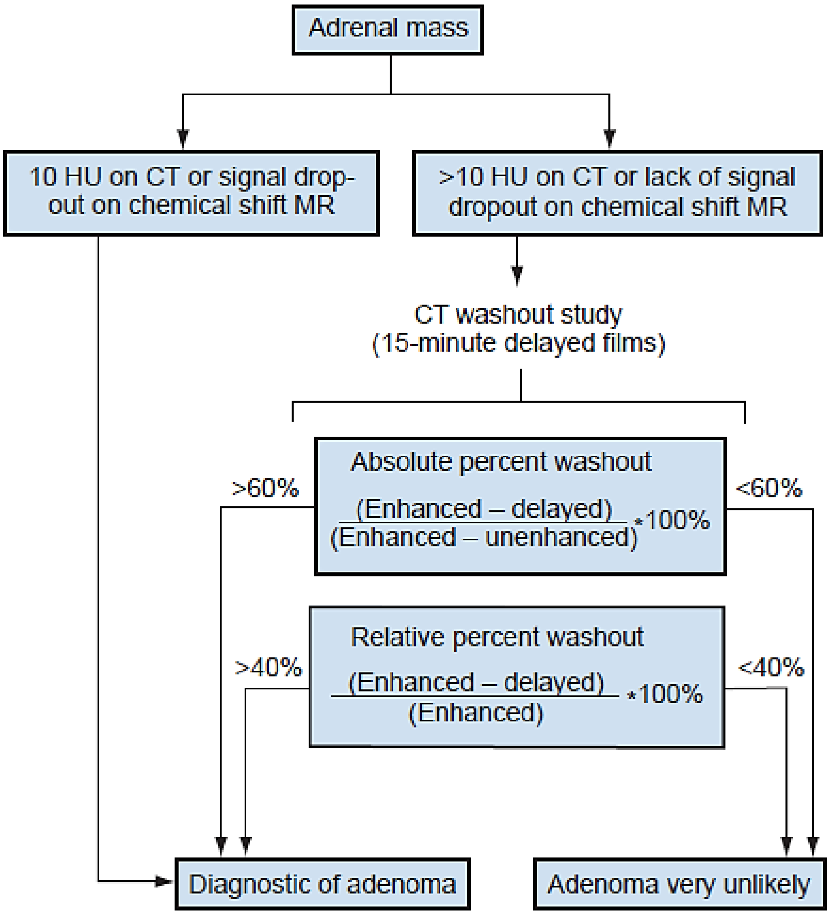

Adrenal mass
10 HU on CT or signal drop-out on chemical shift MR
>10 HU on CT or lack of signal dropout on chemical shift MR
CT washout study
(15-minute delayed films)
Absolute percent washout
(Enhanced – delayed) / (Enhanced – unenhanced) *100%
>60%
<60%
Relative percent washout
(Enhanced – delayed) / (Enhanced) *100%
>40%
<40%
Diagnostic of adenoma
Adenoma very unlikely

Figure 65-29. **Summary of evaluation of adrenal mass using modern cross-sectional imaging. CT, computed tomography; HU, Hounsfield units; MR, magnetic resonance.**

Radionucleotide imaging such as MIBG scan has limited role only in select cases. Similarly 18F-FDG PET scan also has limited role in further evaluation of metastatic disease for staging.

Size and growth kinetics

- A relationship does exist between the size of an adrenal lesion and its malignant potential, with larger masses more likely to exhibit adverse clinical and pathologic features.
- Masses that **exceed 6 cm should be considered malignant until proven benign**, which usually requires definitive resection. Management of incidentalomas between **4 cm and 6 cm** is more controversial. In this intermediate size range, the rate of malignancy is estimated to be **only 6%**. Nonetheless, in otherwise healthy individuals with acceptable perioperative risk profile, most experts recommend 4 cm as the cutoff diameter that warrants resection.

- For lesions smaller than 4cm that are not metabolically active and that appear benign on imaging, Reimaging at 6, 12, and, as possible, 24 months is currently recommended to verify oncologic indolence. A rather arbitrary criterion of **1 cm of growth** has been proposed as an indication for resection; however, the patient must be counseled that the chance of malignancy is low if growth kinetics are flat.

Role of adrenal biopsy: Adrenal biopsy has very limited role in incidentalomas (the very few that cannot be characterised by imaging and if the risk of biopsy will change the management). In the rare instance that it is considered, phaeochromocytoma should be excluded.

Metabolic function evaluation

The metabolic evaluation for incidentaloma includes:

1) Testing for cortisol hypersecretion – Any of the following may be used
    a. Overnight low dose dexamethasone suppresion test – 1mg dexamethasone given at 11PM in the night and sample to be collected between 8AM and 9AM the following morning
    b. 24 hour urinary free cortisol – affected by renal function. Unaffected by oral contraceptives and pregnancy (unlike overnight suppression test)
    c. Late night salivary cortisol test
2) Testing for hyperaldosteronism – this is done in the presence of hypertension and suspecting hyperaldosteronism
    a. Plasma morning aldosternone to renin ratio and plasma aldosterone – ARR (Aldosterone rennin ratio) more than 20 with plasma aldosternone level >15ng/ml is suggestive of hyperaldosteronism – further secondary testing will be needed to confirm diagnosis.
3) Testing for catecholamines – plasma metanephrines or 24 hour urinary fractionated metanephrines.
4) Sex steroids – rarely secreted by incidentaloma. Routine testing not recommended.

A small percentage (**approximately 2%**), of metabolically silent adrenal incidentalomas are reported to show new metabolic activity during follow-up evaluation. The most recent consensus statement by a panel of experts recommends annual **metabolic hormonal screening for the first 3 to 4 years** after diagnosis, especially for masses that are 3 cm in diameter.

The management algorithm for an incidentaloma is as follows:

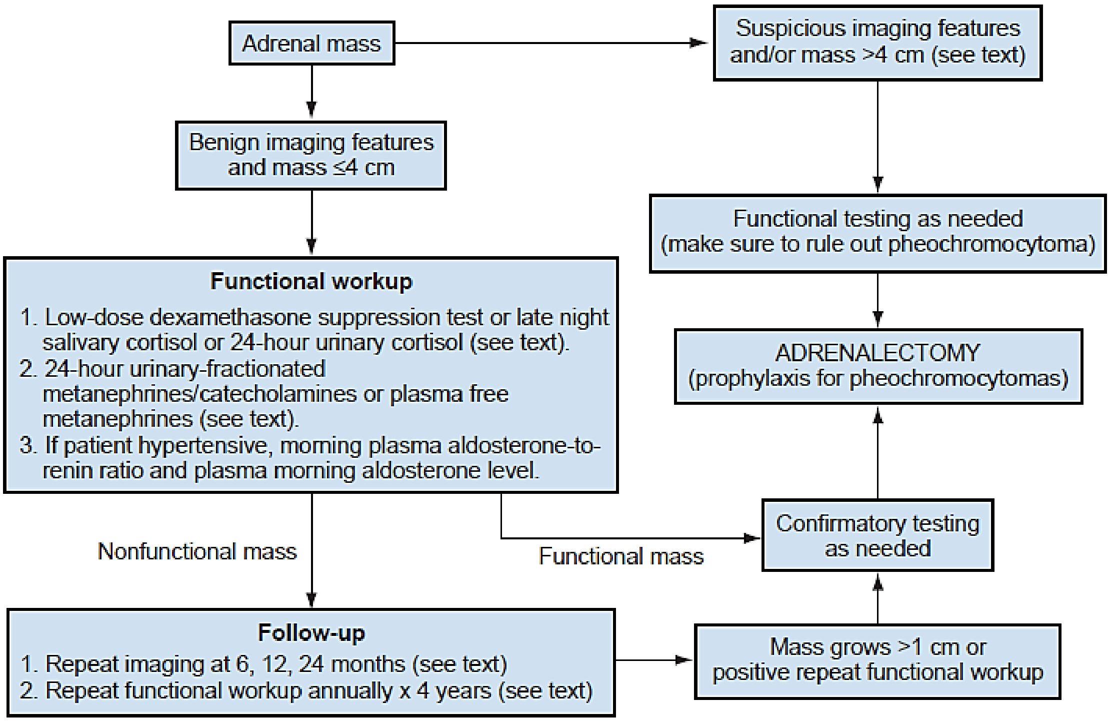

Adrenal mass
Suspicious imaging features and/or mass >4 cm (see text)
Benign imaging features and mass ≤4 cm
Functional testing as needed (make sure to rule out pheochromocytoma)
Functional workup
1. Low-dose dexamethasone suppression test or late night salivary cortisol or 24-hour urinary cortisol (see text).
2. 24-hour urinary-fractionated metanephrines/catecholamines or plasma free metanephrines (see text).
3. If patient hypertensive, morning plasma aldosterone-to-renin ratio and plasma morning aldosterone level.
ADRENALECTOMY (prophylaxis for pheochromocytomas)
Nonfunctional mass
Functional mass
Confirmatory testing as needed
Follow-up
1. Repeat imaging at 6, 12, 24 months (see text)
2. Repeat functional workup annually x 4 years (see text)
Mass grows >1 cm or positive repeat functional workup

Figure 65-33. **Management algorithm for newly diagnosed incidental adrenal mass.**

Benign upper tract

1. Reninoma

AKA Juxtaglomerular cell tumor is a benign tumor of the renal juxtaglomerular cell apparatus, women in the third and fourth decades are most commonly affected

Clinical presentation - hypersecretion of renin and includes hypertension and hypokalemia and associated symptoms such as polydipsia, polyuria, myalgia, and headaches .

Investigations-

- elevated plasma renin activity
- secondary hyperaldosteronism
- hypokalemia
- A solitary renal lesion (radiologic appearance is that of a small (<3 cm) solid hypovascular renal mass)
- Histologic examination reveals sheets of polygonal to spindle-shaped cells, abundant eosinophilic cytoplasm - Strong immunostaining for factor VIII and factor VIII–related antigen; Cells will also stain for renin, CD34, vimentin, and actin.

Treatment – usually NSS because natural history is of benign nature

2. Mechanism of renal failure in ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) progresses to end-stage renal insufficiency before the age of 73 in approximately 48% of affected individuals.

Mechanism:-

- The cysts initiate in early childhood in ***fewer than 1% of renal tubules*** as a consequence of the focal expression of mutated DNA.
- ***Tubule cells proliferate,*** causing segmental dilation, in association with the ***abnormal deposition of extracellular matrix proteins.***
- Most of the cysts separate from the parent tubules and fill with fluid by ***cAMP-mediated chloride secretion.***

Risk factors associated with accelerated loss of renal function include:

- Genotype - ***PKD Type 1*** progresses more rapidly than PKD Type 2
- Gender- ***Males*** progress more rapidly than females
- Race - ***Black*** patients progress more rapidly than white
- Hypertension
- Proteinuria.

➢ The relation between kidney size and progression to renal failure is debated.

Progressive PKD is associated with the cellular expression of

- Proto-oncogenes - fos, myc, ras, erb
- Growth factors - EGF, HGF, acid and basic FGF
- Chemokines - MCP-1. Osteopontin
- Metalloproteinases, and apoptotic markers

- The interstitial accumulation of ***Types I and IV collagen, laminin, fibronectin , macrophages and fibroblasts,*** the magnitudes of which increase with age.
- ***Cyst activating factor (CAF)*** - A neutral lipid identified in cyst fluid that stimulates fluid secretion and proliferation of renal epithelial cells and monocyte chemotaxis, has recently been identified as a potential progression factor.
- In those patients destined to develop renal failure there is loss of non-cystic parenchyma in association with mass replacement by fluid-filled cysts in a network of interstitial fibrosis.
- The decline in renal function is probably the ***consequence of processes leading to interstitial fibrosis, as in other nephropathies,*** rather than due to simple mechanical displacement of parenchyma by cysts.

3. Management of renal trauma (essay)

Renal trauma occurs in approximately 1-5% of all trauma cases

Mode of injury

1. Blunt renal injuries

- Blunt mechanisms include MVAs, falls, vehicle-associated pedestrian accidents and assault.
- In general, renal vascular injuries occur in less than 5% of blunt abdominal trauma, while isolated renal artery injury is very rare ~1% and renal artery occlusion is associated with rapid deceleration injuries.

2. **Pediatric Blunt trauma**

3. Penetrating renal injuries

Please read following update extract.

thrombosis, more severe force may cause a complete avulsion of the pedicle.[11, 14]

Pediatric blunt trauma. In a recent meta-analysis of 95 expectantly managed pediatric patients (age ≤18 years) with blunt, grade IV renal trauma 68 required no interventions throughout the management course.[15] A total of 10 separate, single institution, retrospective cohort studies were included in the final analysis. Children suffering vascular grade IV injuries were excluded from analysis due to variability in management. Surgical exploration was required at some point in the care of 11 patients with most treated successfully with partial nephrectomy or renorrhaphy. A symptomatic urinoma developed in 17% of cases and was managed successfully with ureteral stent placement and/or percutaneous drainage in 81%. Overall, the total or partial renal preservation rate was 95%.

Another review of 419 pediatric patients registered in the National Trauma Data Bank® with grade IV or V injuries confirmed the efficacy of an initial non-operative management approach in appropriate children.[16] Of the patients 81 underwent surgical intervention in the first 24 hours after injury, whereas 338 were initially treated non-operatively. Cases of blunt trauma (vs penetrating) or grade IV (vs grade V) injuries were more likely to be managed successfully via a non-operative approach. Overall, 11% of patients underwent nephrectomy, with an adjusted relative risk of 0.24 (95% CI 0.16 - 0.36) in favor of the conservatively managed group. Of the 338 cases in the expectantly managed group 24 required at least 1 urological intervention during the course, most of which were endoscopic. Angioembolization was required in 6 cases in each group.

In a single institution review of 18 children (mean age 8.4 years, SD 3.4 years) with exclusively grade V renal trauma 9 were treated successfully via a non-operative approach.[17] Five kidneys were salvaged using selective angioembolization (2) or percutaneous nephrostomy drainage (3) on an as needed basis. Overall nephrectomy rate was 22%.

Penetrating trauma. In a large population based study using the National Trauma Data Bank 16% of renal injuries in the U.S. were penetrating.[1] Firearms accounted for 58% and stab wounds 42%. Although MVCs are responsible for the majority of renal trauma, patients presenting with GSW are more likely to have a renal injury (3.5%) than MVC trauma patients (2.2%).[1] Underdeveloped countries with civil unrest have reported series with up to 75% of renal injuries penetrating in nature.[3]

The type and severity of renal injury, risk of associated injuries and effect on surrounding tissues vary significantly between stab wounds, and low and high velocity GSWs.[14] Although they often penetrate much deeper, low velocity bullets tend to result in a similar wound profile as stab wounds, with most of the injury occurring from direct contact with the bullet or knife (crush injury). However, high velocity bullets (>350 m/s) damage tissue in the immediate bullet path by direct contact (crush injury) as well as injure a substantial amount of tissue adjacent to the bullet path through cavitation mechanisms (blast injury), often resulting in delayed tissue necrosis.[14] For this reason, care should be taken to debride any questionable tissue adjacent to the path of a high velocity bullet.

Similar to the mechanism of injury, the location of penetration can be predictive of injury severity. Penetrating injuries anterior to the anterior axillary line more often result in higher grade injuries since the renal pedicle, hilum and renal pelvis are in close vicinity.[14] Concomitant abdominal organ injuries are more common with anterior lesions as well. Flank wounds, especially stab wounds posterior to the anterior axillary line, generally result in a lower grade, more peripheral parenchymal injuries.[14]

Pediatric penetrating trauma. As penetrating renal injury is fortunately a relatively rare event in the pediatric population, literature guiding its management has primarily been limited to small retrospective studies and subgroup analyses. Low grade penetrating isolated renal injuries in children can often be safely managed non-operatively. Hemodynamically stable children with high grade penetrating renal injuries can be considered candidates for initial non-operative treatment but a significantly higher percentage will require operative or endoscopic intervention than children suffering from blunt trauma.[16]

EVALUATION

Initial evaluation. The initial evaluation of any trauma patient should begin with the American College of Surgeons Acute Life Support primary survey algorithm which includes airway, breathing, circulation (external bleeding control), disability (neurological status) and exposure (undress)/environment (temperature control). While resuscitation with oxygen and intravenous colloid infusion is initiated and monitoring devices such as electrocardiogram, pulse-oximetry and blood pressure are being established, the urethra, perineum and rectum should be evaluated. The flank should be inspected for ecchymosis and flank pain, and the presence of a ‘‘seat belt sign’’ should be noted on the abdomen, since all of these physical findings indicate significant trauma and possible renal injury.[14] If there are no abnormal findings a urine sample should be obtained to evaluate for microscopic or gross hematuria. Blunt and penetrating trauma to the genitourinary tract commonly results in hematuria but its presence or degree does not necessarily correlate with injury location or severity.

Indications for imaging. **The decision to image depends on the severity and mechanism of injury (blunt/penetrating), presence of hematuria (gross/microscopic) and shock (systolic blood pressure <90 mm Hg). The combination of blunt trauma with gross hematuria or with microscopic hematuria and shock requires imaging.[18] Stable blunt trauma patients with microscopic hematuria may be ob-**

served without imaging, unless they suffered a major acceleration or deceleration injury such as a fall from a great height or high speed MVC.[18] These patients may have a severe deceleration type of injury and imaging should always be performed. Radiographic or surgical staging should be performed in cases of penetrating trauma and a stab/bullet wound in a location concerning for intra-abdominal organ injury or any degree of hematuria.[14]

For blunt abdominal trauma, imaging should be performed in any stable child with gross hematuria or significant microscopic hematuria (>50 red blood cells per high power field) and shock (systolic blood pressure <90 mm Hg). However, the late manifestations of shock in children with traumatic injuries have led some experts to recommend imaging in any stable child with microscopic hematuria >50 red blood cells with or without shock.[19] **Additionally, any child with a significant associated injury or a suspicious mechanism of injury such as a rapid deceleration, high velocity strike, fall from >15 feet or a direct blow to the abdomen or flank should be imaged regardless of the presence of hematuria.**[20] All clinically stable children with penetrating abdominal or pelvic trauma should undergo radiographic assessment.

Imaging modalities. CT: Contrast enhanced CT with additional 10-minute delayed scan is the ‘‘gold standard’’ imaging modality for staging a stable trauma patient.[21] **Trauma patients lacking radiographic signs of renal injury who do not have any perinephric, periureteral or pelvic fluid collections do not require delayed imaging per expert consensus. If any of these subtle findings, especially low density fluid tracking around the kidney and down the ureter, are present on the initial contrast enhanced CT a UPJ or a ureteral injury can easily be missed if delayed images are not obtained.**[22]

The ability of CT scanners to quickly evaluate solid organ and vascular injuries has significantly improved the management of trauma. Important radiological findings that should be noted when reviewing CT for renal trauma include arterial medial extravasation of contrast, denoting a severe arterial injury; medial hematoma without arterial extravasation, often secondary to a venous injury; differential contrast uptake and excretion, which is indicative of arterial injury or thrombosis; cortical rim sign, often indicative of a main renal artery injury; degree of parenchymal laceration and involvement of the collecting system; degree of devitalized tissue; and the size and location of a perinephric hematoma or fluid collection.[21] Medial extravasation of contrast is often seen with UPJ ruptures and no contrast will be seen in the distal ureter on delayed images of complete UPJ avulsion. Historically diagnosis of UPJ injuries was delayed in 50% of cases but routine evaluation of trauma with CT, especially when delayed images are obtained, has increased the initial detection rate to almost 90%.[22]

Debate continues regarding the necessity of repeat CT scan 36 to 72 hours later for conservatively managed renal injuries. According to expert opinion, repeat imaging is not required for grade 1/2 injuries and grade 3 injuries without hemodynamic instability or devitalized fragments. Some authors are now beginning to advocate against routine repeat imaging for grade 4/5 renal injuries when there is no **clinical indication (eg sepsis, decrease in hematocrit, unstable blood pressure, increasing hematuria or oliguria), arguing that repeat scans rarely change the management of this population and that kidneys with stable or improved appearance on repeat CT still have a delayed complication rate of 25%.**[23, 24] Other authors have questioned these findings and expressed concern regarding inconsistencies in the timing of repeat imaging, grading of the images, use of ultrasound for follow-up imaging in many patients and the small size of the study cohort.[25, 26] Future studies will hopefully help define the indications for follow-up imaging of high grade renal trauma.

As children are thought to be significantly more sensitive to the carcinogenic effects of radiation and have a significantly longer life expectancy than adults, care should be taken to use the minimum necessary dosage to achieve adequate assessment of the trauma.[27, 28] A pediatric trauma patient undergoing trauma oriented CT within the first 24 hours of injury absorbs 11.4 mSv, with children transferred to trauma centers from smaller hospitals receiving a higher number of scans and greater doses of radation.[29]

Angiography: Approximately 2% of trauma patients presenting with a renal injury undergo diagnostic angiography, and 47% of them receive concomitant embolization.[30]

Intravenous Urography: Although almost completely replaced by CT for evaluating stable trauma patients, the intravenous urogram still maintains a role in evaluating the unstable trauma patient taken directly to the operating room by verifying the presence of a contralateral kidney (**1 shot urogram with 2 ml/kg body weight bolus followed by plain film 10 minutes later).** Identifying a functional contralateral kidney is important first because every possible attempt should be made to save the injured kidney if it is the only one. The injured kidney may lack contrast uptake if there is a major vascular injury or demonstrate a delayed nephrogram from significant compression from a contained hematoma. An abnormal renal outline, displacement of the bowel or ureter and loss of the psoas margin are all suggestive of renal injury and hematoma.[31] Distinctive patterns of contrast extravasation that should raise concern of a possible UPJ injury include extravasation medial or circumferential (circumferential urinoma) to the kidney.[32] Also, with a complete UPJ disruption, the ipsilateral ureter will lack intraluminal contrast.

Ultrasound: The Focused Assessment by Sonography for Trauma is often used to evaluate trauma patients for abdominal injuries and intra-abdominal fluid collections. Despite the availability and low risk nature of sonography, this modality has a low sensitivity (48%) for detecting renal injuries and often overlooks significant damages.[33] The use of contrast enhanced ultrasound has recently been reported to increase the sensitivity to 69%, which is still inferior to the > 90% sensitivity of CT.[34]

TREATMENT

Non-operative. To reduce the risk of nephrectomy and maintain maximal functioning parenchyma, the current consensus is to treat stable patients with grade III and grade IV lesions conservatively.[14] Nephrectomy has been shown to increase the likelihood of renal failure and potentially cardiac disease.[35] Also, patients with mild to moderate trauma who underwent renal exploration had twice the risk of developing a complication than those with similar injuries who did not undergo exploration (7.1% vs 3.3%), further emphasizing the important role of conservative management when appropriate.[35]

Several recent European studies have further verified favorable outcomes with conservative management, with only 1 of 23 (4%) cases of grade III/IV lesions requiring open surgery in 1 study, and half of the cases with grade IV lesions and active urinary extravasation successfully managed conservatively in another study (37% required ureteral stent placement and 15% open surgery).[10, 36] However, in another study absence of contrast material in the ipsilateral ureter, a large separation of the upper and lower poles, multiple areas of extravasation and transfusion requirements were associated with failure of conservative management.[37] Interestingly, there was no association between diameter/location of extravasation and failure of conservative management. Retrograde ureteral stent placement has recently been advocated only for patients with pain from ureteral clot obstruction (suspected by clinical findings and confirmed with CT), fever >38.5°C or significant urine leakage on repeat imaging 3 to 5 days later defined as an increasing urinoma or absence of ureteral opacification.[36] Successful conservative management for up to 51.8% of grade V injuries has been reported.[38]

The rate of obligatory exploration of penetrating renal trauma has decreased as well. An increasing number of studies evaluating conservative management of penetrating renal trauma have demonstrated acceptable outcomes, initially with stab wounds and more recently with GSWs. Conservative management was performed in 42% of 1856 cases of abdominal GSWs.[39] All of these patients were hemodynamically stable and initially lacked peritioneal signs, and surprisingly peritoneal signs requiring laparotomy developed in only 4%. In another series, when all types of penetrating injuries were combined, an initial attempt at conservative management was reported in 49 of 75 cases, including grade 4 injuries in 9.[40] A retrospective analysis of the records of 889 penetrating and blunt renal trauma cases revealed an increased risk of local kidney related complications after renorrhaphy than after conservative management or partial or total nephrectomy.[35] Some authors recommend against renal exploration in patients undergoing laparotomy for penetrating injuries if there is a stable hematoma away from the hilum.[41]

Operative. Even in the midst of a paradigm shift away from operative intervention for renal injuries, there are many situations when surgery is still indicated. Absolute indications for renal exploration are life threatening hemorrhage believed to be from renal injury, renal pedicle avulsion and expanding, pulsatile or uncontained retroperitoneal hematoma.[42] Relative indications include incomplete radiographic staging with concurrent traumatic injuries that require repair/exploration, extensive devitalized renal parenchyma, vascular injury and urinary extravasation. **Patients in shock or who require a high 24-hour transfusion rate, as well as those with a penetrating injury, higher grade laceration, large perirenal hematoma, intravascular contrast extravasation, medial renal laceration or multiple concurrent intra-abdominal injuries are more likely to undergo nephrectomy or require urgent hemostatic intervention after renal trauma.**[9, 43]

With continued research into the outcomes and cost of different management schemes for renal trauma, there will undoubtedly be ongoing revision of treatment algorithms. The recent addition of nomograms to predict the need for renal exploration may further advance our understanding of risk factors. When the AAST kidney injury scale, mechanism of injury, need for transfusion, blood urea nitrogen level and serum creatinine are considered, Shariat et al designed a nomogram that accurately predicted the need for renal exploration in 96.9% of cases.[44] The impact advances like this will have on clinical management of renal trauma has yet to be seen.

Embolization. Percutaneous transluminal angiographic embolization has proven to be effective for ongoing renal hemorrhage after blunt or penetrating trauma,[45] particularly in unstable patients with active extravasation and after failed conservative management. Success rates between 80% and 100% have been reported, and the ability to catheterize interlobar arteries with a maximum diameter of 1 mm has increased the amount of functioning nephrons remaining after a superselective embolization procedure.[46]

Breyer et al noted an 81% success rate of AE for grades 3 and 4 blunt and penetrating renal trauma, with much poorer results for grade 5 injuries.[45] **They concluded that embolization should be the initial treatment for patients with grades 3 and 4 lacerations, arteriovenous fistula or pseudoaneurysm with persistent bleeding** (fig. 1). Although initial success with embolization for grade 5 renal lacerations has been reported in small case series, a larger review of the National Trauma Data Bank indicated a need for several consecutive interventions before adequate hemostasis was attained with grade IV/V lesions.[30, 47] Still, less than 20% of grade IV/V injuries required nephrectomy, and the impor-

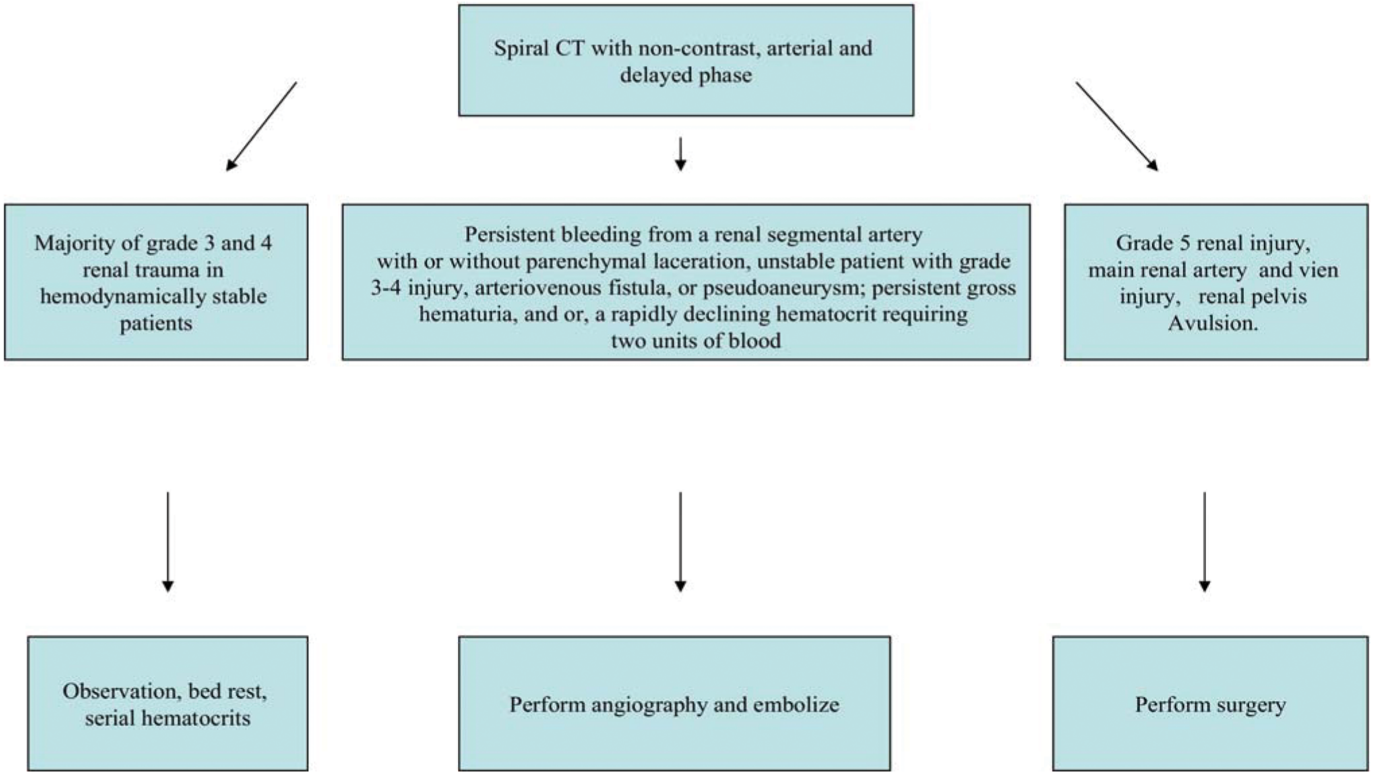

Spiral CT with non-contrast, arterial and delayed phase
Majority of grade 3 and 4 renal trauma in hemodynamically stable patients
Persistent bleeding from a renal segmental artery with or without parenchymal laceration, unstable patient with grade 3-4 injury, arteriovenous fistula, or pseudoaneurysm; persistent gross hematuria, and or, a rapidly declining hematocrit requiring two units of blood
Grade 5 renal injury, main renal artery and vien injury, renal pelvis Avulsion.
Observation, bed rest, serial hematocrits
Perform angiography and embolize
Perform surgery

Figure 1. Suggested management strategies for children and adults with renal trauma.

tance of following patients with high grade renal injuries closely after initial embolization was emphasized.[30] A recently published intermediate follow-up of 10 patients after AE for grade 5 injuries indicated promising results, further confounding the picture.[48] Larger studies are definitely needed to clarify the role of AE with grade 5 injuries. Another issue brought to attention by the National Trauma Data Bank review was the possible overuse of AE for low grade lesions. Up to 37% of patients undergoing diagnostic angiography and 22% of those undergoing subsequent embolization had AAST grade I/II lesions, highlighting the need for national agreement on the use of these procedures.[30]

Indications for AE are debated in the literature but generally include active extravasation in the setting of declining clinical status. Several studies have recently suggested other criteria to help determine the need for AE, including perirenal hematoma size or rim distance, intravascular contrast extravasation and discontinuity of Gerota's fascia.[49, 50] **Conversely, absence of intravascular contrast extravasation with a perirenal hematoma rim distance of <25 mm has been shown to exclude the need for interventional radiology, even for patients who required transfusion.**[51]

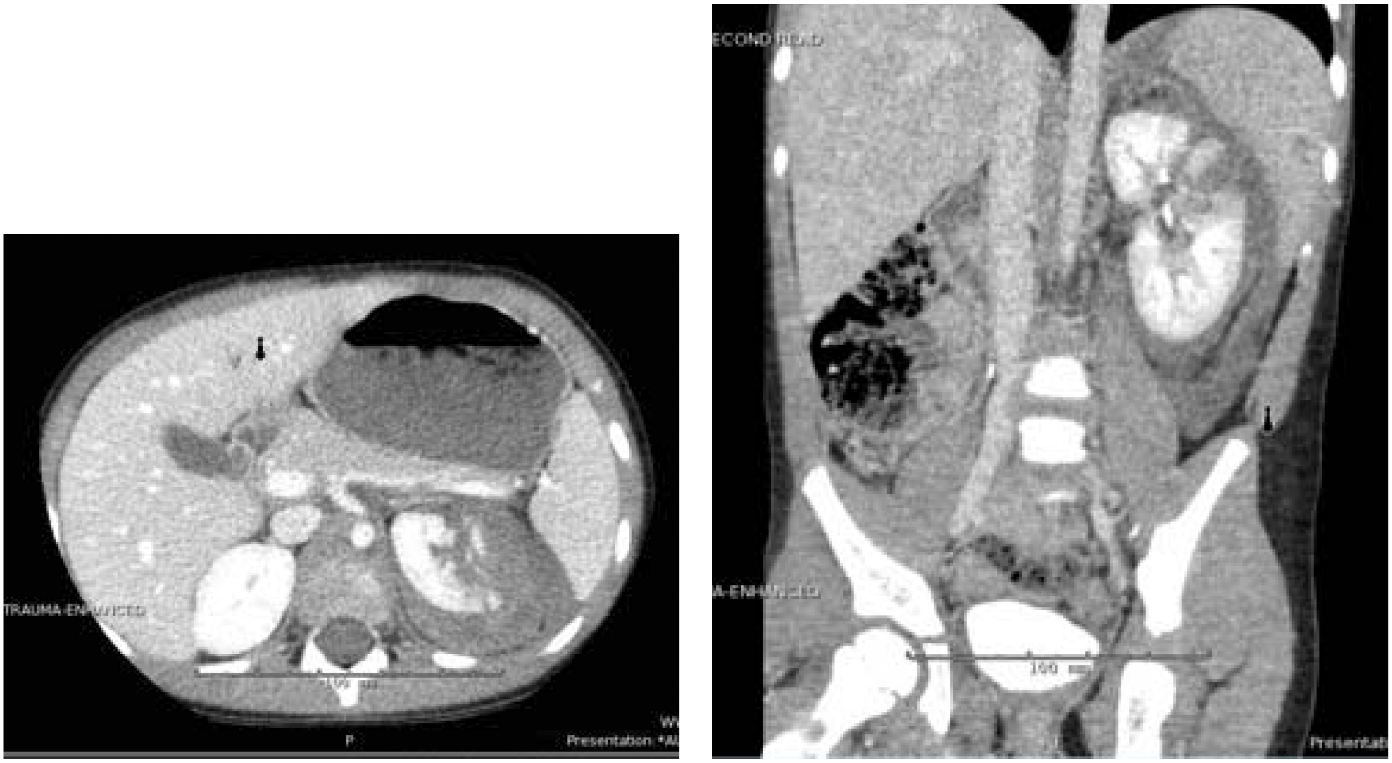
COMPLICATIONS

Extravasation/urinoma. The prevalence of urinary extravasation is higher after penetrating injury (10% to 30%) than after blunt trauma (2% to 18%).[52] By definition it is associated with grade IV/V injuries and generally resolves in most patients without intervention (75% to 90%).[52, 53] Severe renal pelvic lacerations and UPJ disruptions should be surgically repaired but are uncommon. For persistent cases, the use of a retrograde stent or percutaneous nephrostomy typically resolves the issue. Direct percutaneous drainage of urinomas is rarely necessary.[53]

Urinary extravasation will resolve spontaneously in 66% to 85% of children with grade IV renal injuries.[15, 37, 54] **However, cases of persistent or worsening extravasation, adynamic ileus, fever or persistent flank pain may benefit from endoscopic or percutaneous management. Approximately 80% to 100% of these patients will respond to minimally invasive therapies such as nephrostomy tube placement or ureteral stenting without requiring open exploration.**

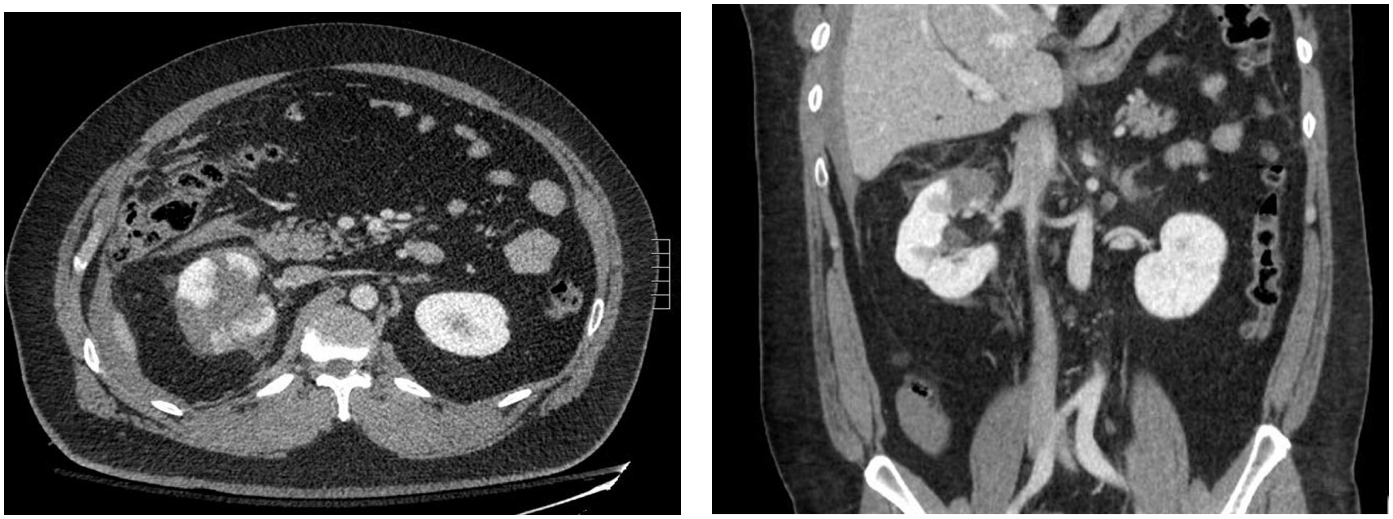
Arteriovenous fistula. Posttraumatic arteriovenous fistulas are rare (0% to 7%) and are typically seen after penetrating trauma.[55] Clinical manifestations vary by size and location but often include varying degrees of hematuria and cardiovascular problems including diastolic hypertension, cardiomegaly and congestive heart failure. An abdominal bruit can sometimes be appreciated on abdominal examination. Contrast enhanced CT usually effectively diagnoses arteriovenous fistulas but magnetic resonance angiography may be slightly more sensitive.[56] Angiography with superselective AE is generally a safe and effective treatment modality.[57]

Pseudoaneurysm. Like arteriovenous fistula, pesudoaneurysms generally occur after penetrating renal trauma. They can grow over time and occasionally erode into the surrounding



A. *B.*

Figure 2. Left grade III renal laceration and concomitant grade II splenic laceration in 3-year-old boy who fell from 10 feet onto left flank. Axial (*A*) and coronal (*B*) cuts of CT urogram reveal no evidence of extravasation. Hematuria resolved by hospital day 2, hematocrit remained stable and patient was discharged home with activity precautions on hospital day 3.



A. *B.*

Figure 3. Axial (*A*) and coronal (*B*) images of CT urogram of 48-year-old man after GSW to anterior lateral abdominal wall reveal grade IV renal laceration with no active extravasation of blood or urine. Bullet tracked inferomedially through liver, gallbladder, right upper pole of right kidney and duodenum. Right colon had been reflected, and minimal retroperitoneal hematoma was encountered when retroperitoneum was entered by trauma service during initial exploration. Limited right renorrhaphy was performed to reapproximate obvious defect in superior renal capsule. Trace urinary extravasation from calyceal injury was noted on CT performed on postoperative day 5 and was managed conservatively since there was no significant associated fluid collection. There was no perinephric fluid seen on renal ultrasound on postoperative day 9 and patient remained clinically stable until discharge home.

pelvicaliceal system or perinephric tissue. Pseudoaneurysms generally present with flank pain, hematuria, abdominal bruit or hypertension. Contrast enhanced CT is most often the study of choice but Doppler ultrasound may identify a pseudoaneurysm as an anechoic lesion with characteristic ''to-and-fro'' swirling.[58] Angiography with embolization is the gold standard for definitive diagnosis and treatment.

Secondary hemorrhage. One of the most serious complications of renal trauma, secondary hemorrhages generally occur 2 to 3 weeks after penetrating deep cortical lacerations.[59] Most cases of delayed bleeding are thought to be caused by an traumatic arteriovenous fistula or pseudoaneurysm, or from injured segmental arteries initially tamponaded by hematoma formation that begin to bleed with liquefaction of the hematoma.[52] Bleeding may be into the collecting system or perirenal space and can be life threatening. Emergency AE is indicated.

Hypertension. Development of hypertension after renal trauma is a controversial issue with varied results from multiple studies. Although some studies indicate an increased incidence of hypertension with conservative management, others indicate equal incidence between conservatively and surgically treated patients. Transient hypertension, which resolves in 12 to 50 days, is seen in 6% to 10% of patients.[52] Chronic hypertension develops in a period ranging from 2 days to 32 years, which is why patients with a history of renal trauma should undergo long-term yearly blood pressure monitoring.[52]

PREVENTION

The ongoing study of the epidemiology of renal trauma has prompted various efforts to educate the population about preventive measures to avoid renal injuries. Also, research and development of many innovative safety measures to help prevent accidents that result in renal trauma and provide better protection when they do occur continue to be developed. Since approximately 70% of blunt renal trauma results from MVCs, significant resources have been appropriated to educate and encourage the use of seat belts as well as develop safer automobiles and roadways.[60] Implementation of frontal and side air bags into most vehicles produced today has significantly decreased the risk of renal injury (45.3% and 52.8% reduction, respectively).[61] The Centers for Disease Control and Prevention injury center currently funds 11 programs that collaborate to reduce the incidence and severity of traffic accidents, and vast improvements have been made in multiple areas. In 2010 a total of 32,885 people died of a MVC in the United States, representing a 2.9% reduction from 2009 and the lowest number of fatalities since 1949.[62]

Injuries sustained from bicycle related accidents contribute significantly to the trauma population as 57 million of the U.S. population older than 16 years ride bicycles on a daily basis. A review of the National Electronic Injury Surveillance System database estimated that 43,542 of all genitourinary injuries presenting to U.S. emergency departments from 2002 to 2010 were related to bicycle riding.[63] In an effort to decrease the incidence of MVC vs bicycle accidents, metropolitan areas continue to design bicycle lanes to move cyclists out of the roadway and signs to remind motorists to be cognizant of cyclists.[64]

The use of all-terrain vehicles in the general and pediatric populations has continued to increase in the last 20 years and, not surprisingly, they are responsible for an increasing number of renal injuries and deaths each year.[65] Government legislation, multiple public awareness campaigns, improved safety labeling and age appropriate recommendations from numerous organizations are combating this growing problem.[66]

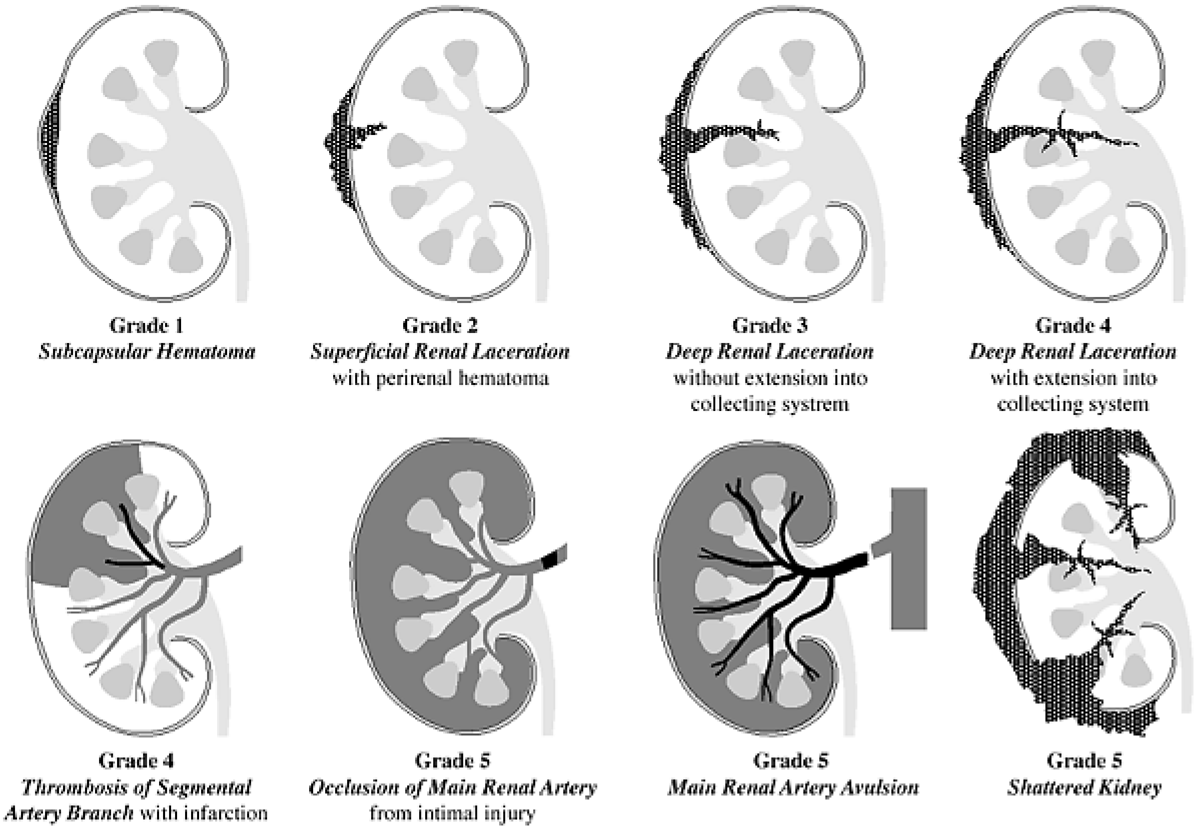
Finally, the recognition of violence as a public health problem has resulted in multiple evidence-based strategies and programs to reduce violence, especially in youths, and highlight the cost-effectiveness of monetary allocations aimed at prevention instead of incarceration.[67]

A fair amount of debate has centered on the participation of children with a solitary, healthy kidney in contact sports, although children are more likely to suffer renal injuries from cycling than from collision sports. Most experts believe that the activity of children with healthy, solitary kidneys should not be limited.[68]

Appendix. American Association for the Surgery of Trauma Kidney Injury Scale[6]

Grade	Type of Injury	Description of Injury
I	Contusion	Microscopic or gross hematuria, urological studies normal
	Hematoma	Subcapsular, non-expanding without parenchymal laceration
II	Hematoma	Non-expanding perirenal hematoma confined to renal retroperitoneum
	Laceration	<1.0 cm parenchymal depth of renal cortex without urinary extravasation
III	Laceration	>1.0 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla and collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum with devascularization of kidney

Additional images which can be drawn in the exam- line diagram chosen!



Grade 1
Subcapsular Hematoma

Grade 2
Superficial Renal Laceration with perirenal hematoma

Grade 3
Deep Renal Laceration without extension into collecting systrem

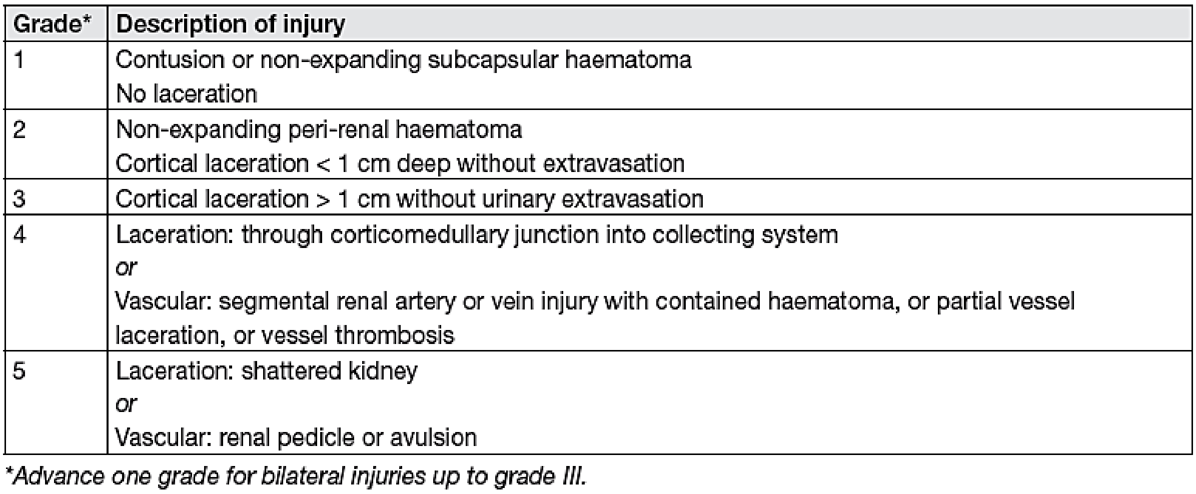
Grade 4
Deep Renal Laceration with extension into collecting system

Grade 4
Thrombosis of Segmental Artery Branch with infarction

Grade 5
Occlusion of Main Renal Artery from intimal injury

Grade 5
Main Renal Artery Avulsion

Grade 5
Shattered Kidney



Grade*	Description of injury
1	Contusion or non-expanding subcapsular haematoma No laceration
2	Non-expanding peri-renal haematoma Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation
4	Laceration: through corticomedullary junction into collecting system *or* Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney *or* Vascular: renal pedicle or avulsion

**Advance one grade for bilateral injuries up to grade III.*

Remember!! Indications for Renal Imaging

The criteria for radiographic imaging include the following:

1. All penetrating trauma with a likelihood of renal injury (abdomen, flank, or low chest entry/exit wound) who are hemodynamically stable enough to have a CT (instead of going right to the operating room or angiography suite).
2. All blunt trauma with significant acceleration/deceleration mechanism of injury.
3. All blunt trauma with gross hematuria
4. All blunt trauma with microhematuria and hypotension (SBP<90 mm Hg at any time during evaluation and resuscitation)
5. All pediatric patients with greater than 5 RBCs/HPF

4. Circumcaval ureter

A circumcaval ureter is a rare congenital anomaly usually associated with upper urinary tract stasis and an ‘‘S’’ or ‘‘fishhook’’ deformity of the ureter, in which the ureter itself passes behind the inferior vena cava. The circumcaval ureter is caused by an abnormal embryological development of the inferior vena cava (IVC).

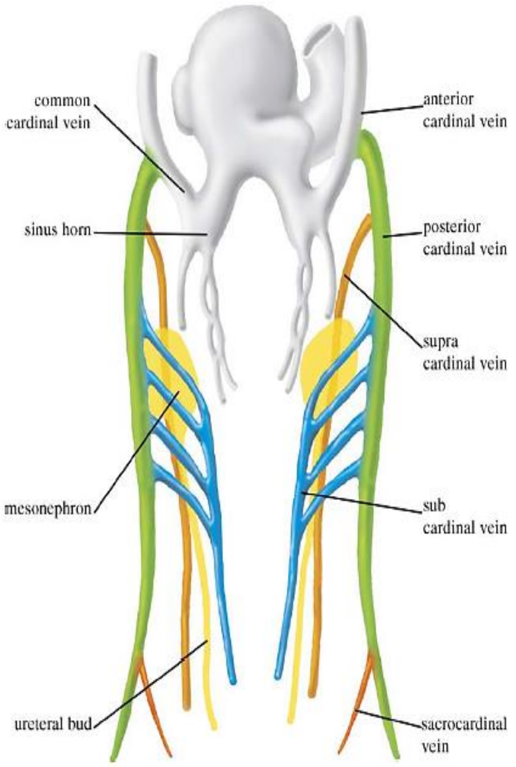


Fig. 3 – Venous system in human embryo at the sixth week.

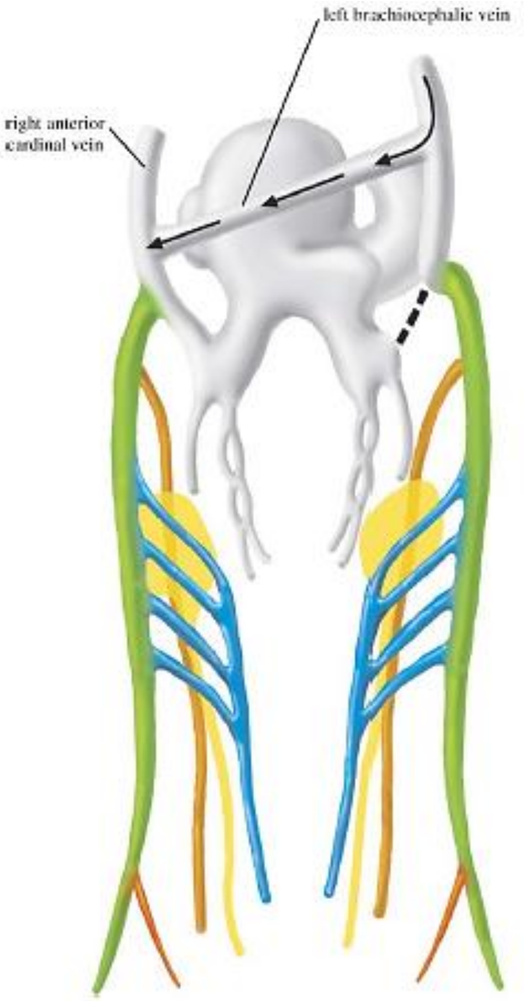


Fig. 4 – Development of the superior vena cava.

During the sixth week the supracardinal veins, which drain the body wall by way of the intercostals veins and take over the functions of the posterior cardinal veins, are formed. The supracardinal veins lie medially to the posterior cardinal veins, laterally to the subcardinal veins, and dorsally to the developing ureter (Fig. 3). Formation of the vena cava system is characterised by the appearance of anastomoses between left and right such that the blood from the left is channelled to the right side. The superior vena cava is formed by the right common cardinal vein and the proximal portion of the right anterior cardinal vein

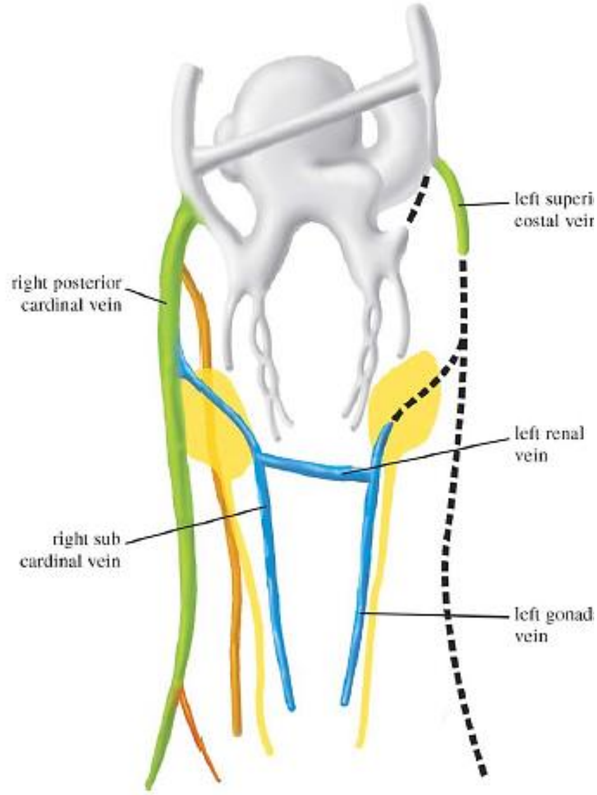


Fig. 5 – Development of the renal segment of the inferio vena cava.

The anastomosis between the subcardinal veins forms the left renal vein. When this communication has been established, the left subcardinal vein disappears,andonly its distal portion remains as the left gonadal vein. Hence the right subcardinal vein becomes the main drainage channel and develops into the renal segment of the IVC (Fig. 5). The anastomosis between the sacrocardinal veins forms the left common iliac vein. The right sacrocardinal vein becomes the sacrocardinal segment of the IVC. The right vitelline vein forms the hepatic segment of the IVC.

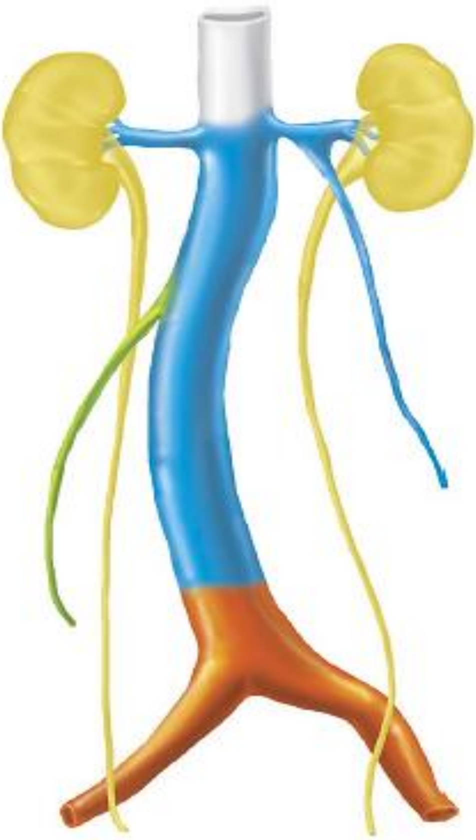


Fig. 6 – The venous system at birth showing the three components of the IVC: hepatic (grey), renal (blue), and sacrocardinal (red) segments.

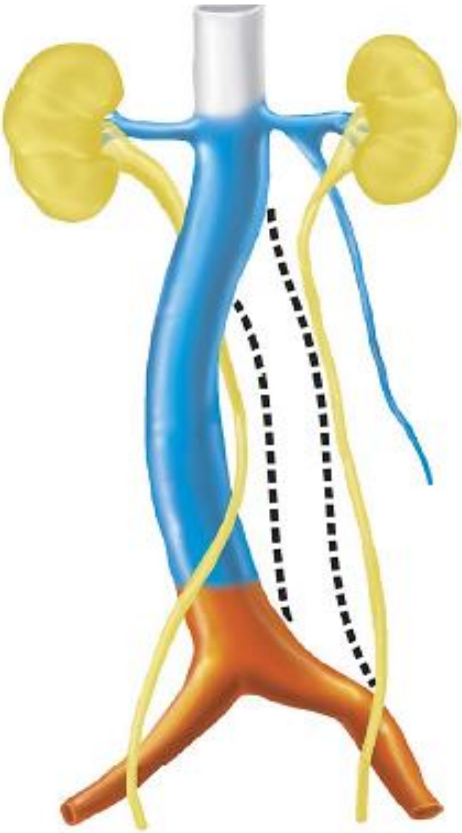


Fig. 7 – Circumcaval ureter.

If the right posterior cardinal vein, which is lateral to the definitive ureteral position, rather than the right subcardinal vein persist as the renal segment of the IVC, a circumcaval ureter would result.

Treatment- Classically open ureteroureterostomy had been the gold standard .

Others- laparoscopic ureteroureterostomy and pyelopyelostomy

5. AML

Angiomyolipoma accounts for ***less than 10% of renal tumors -*** It is typically a "triphasic" tumor composed of varying amounts of 3 elements (dysmorphic blood vessels, smooth muscle components, and fatcells).

- It is a benign neoplasm consisting of thick-walled aneurysmal vessels, smooth muscle, and varying levels of mature adipose tissue.
- Angiomyolipoma is now considered to be of ***neural crest origin, possibly derived from perivascular epithelioid cells (PEC).***
- Angiomyolipoma is the most common renal neoplasm associated with ***spontaneous perirenal haemorrhage***

Genetics :

- These tumors are most often sporadic but can also be associated with the ***autosomal dominant tuberous sclerosis complex (TSC).***
- Twenty to 30 percent of angiomyolipomas are in patients with TSC, and approximately 50% of patients with TSC develop angiomyolipomas.
- TSC-associated angiomyolipomas typically present at
- Younger age (mean age 30 years);
- Less female to- male predominance (2 : 1)
- Multiple, bilateral, and symptomatic tumors.

COMPLICATION :

- The Wunderlich syndrome, or massive retroperitoneal hemorrhage, - most significant complication of renal angiomyolipoma, was reported in up to 10%
- Associated with significant morbidity and potential mortality if not promptly treated.
- Pregnancy appears to increase the risk of haemorrhage from angiomyolipoma.

DIAGNOSIS :

- The presence of fat ***(confirmed on non enhanced thin-cut CT by a value of −20 Hounsfield Units [HU] or less)*** within a renal lesion is considered the diagnostic hallmark.
- Ultrasonography -- well-circumscribed, **highly echogenic lesion** with shadowing.
- Angiography (or CT-angiography) ***aneurysmal dilation is found in 50%*** of angiomyolipomas.
- MRI can be used in difficult cases or in lieu of CT, with ***findings on fat-suppressed images*** being highly suggestive of the diagnosis

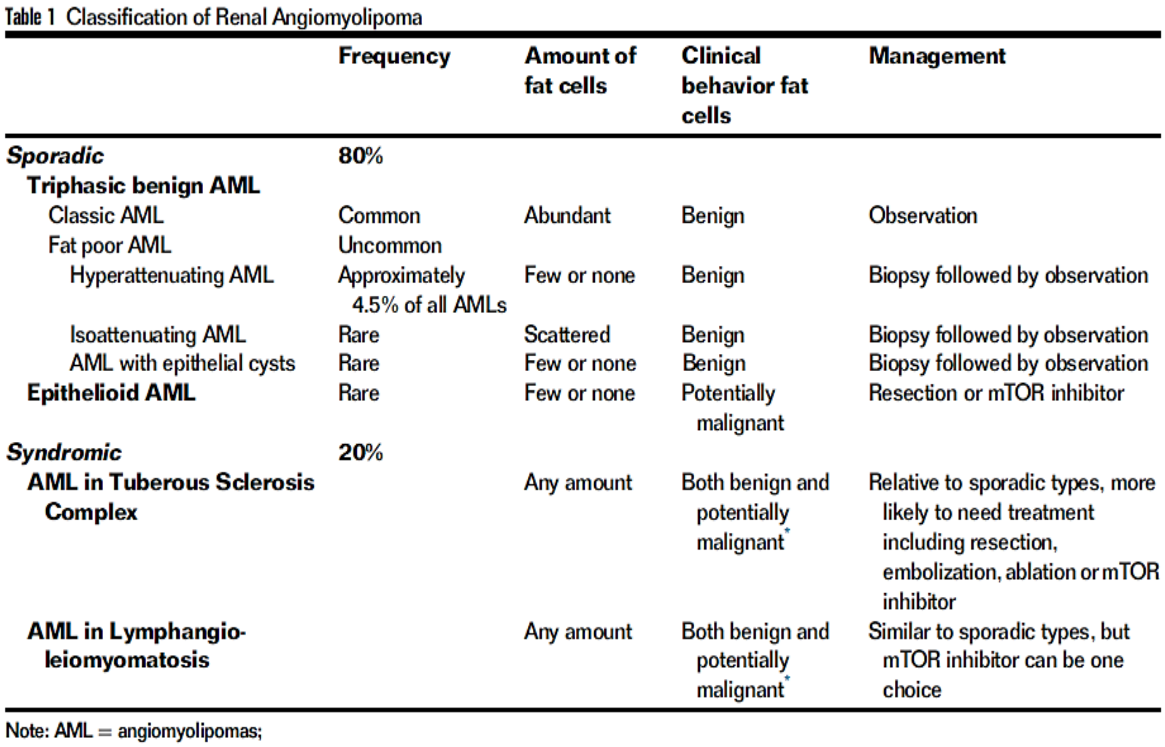


Table 1 Classification of Renal Angiomyolipoma

	Frequency	Amount of fat cells	Clinical behavior fat cells	Management
Sporadic	**80%**			
Triphasic benign AML				
Classic AML	Common	Abundant	Benign	Observation
Fat poor AML	Uncommon			
Hyperattenuating AML	Approximately 4.5% of all AMLs	Few or none	Benign	Biopsy followed by observation
Isoattenuating AML	Rare	Scattered	Benign	Biopsy followed by observation
AML with epithelial cysts	Rare	Few or none	Benign	Biopsy followed by observation
Epithelioid AML	Rare	Few or none	Potentially malignant	Resection or mTOR inhibitor
Syndromic	**20%**			
AML in Tuberous Sclerosis Complex		Any amount	Both benign and potentially malignant*	Relative to sporadic types, more likely to need treatment including resection, embolization, ablation or mTOR inhibitor
AML in Lymphangioleiomyomatosis		Any amount	Both benign and potentially malignant*	Similar to sporadic types, but mTOR inhibitor can be one choice

Note: AML = angiomyolipomas;

Differential diagnosis

- Liposarcoma,
- Fat-containing RCC, and
- Fat poor angiomyolipoma resembles an RCC.

Positive immunoreactivity for HMB-45, a monoclonal antibody raised against a melanoma-associated antigen, is characteristic for angiomyolipoma and can be used to differentiate this tumor from sarcoma and other tumors.

Treatment

- Treatment must be individualized, based on the presentation, pregnancy status, tumor size, and renal function.
- The treatment of choice in cases of acute hemorrhage is ***selective renal angioembolization***.
- Treatment options for elective management of larger angiomyolipomas include ***selective renal angioembolization and open or minimally invasive partial nephrectomy***.
- Embolization is associated with a high rate of secondary procedures
- Preservation of renal tissue remains a priority in those with TSC or multicentric angiomyolipoma and particularly in patients with underlying renal insufficiency.

6. Tuberous sclerosis complex

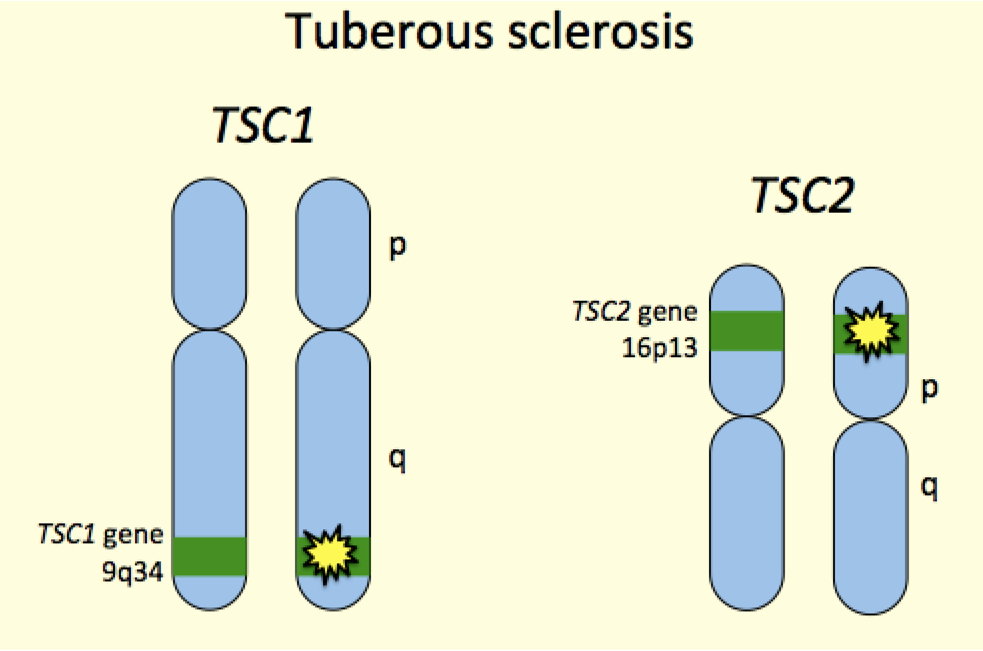
It is otherwise called as Bourneville disease,genetic disorder,Autosomal dominant

Incidence - 1 in 6,000 & 1 in 14,500

Characterized by

- **Epilepsy, mental retardation, adenoma sebaceum**
- **Renal cyst(20%)** – multiple/bilat
- RCC (2%)
- Renal AMLs occur in 40% to 80% of patients with TSC
- Angiomyolipoma (40-80%)- multiple/bilat
- Cranial calcification- subependymal nodules
- Lesions of adenoma sebaceum are flesh-colored papules of angiofibroma -- “ash leaf” spot & Shagreen patch

Genetics



- Autosomal dominant
- **Two genes, *TSC1* on chromosome 9** & ***TSC2* on chromosome 16**

Histopathology - Cysts are linied by hypertrophic, hyperplastic eosinophilic cells

Clinical Features and Prognosis - Renal cysts develop in 20% of patients and most often manifest before 3 years of age.

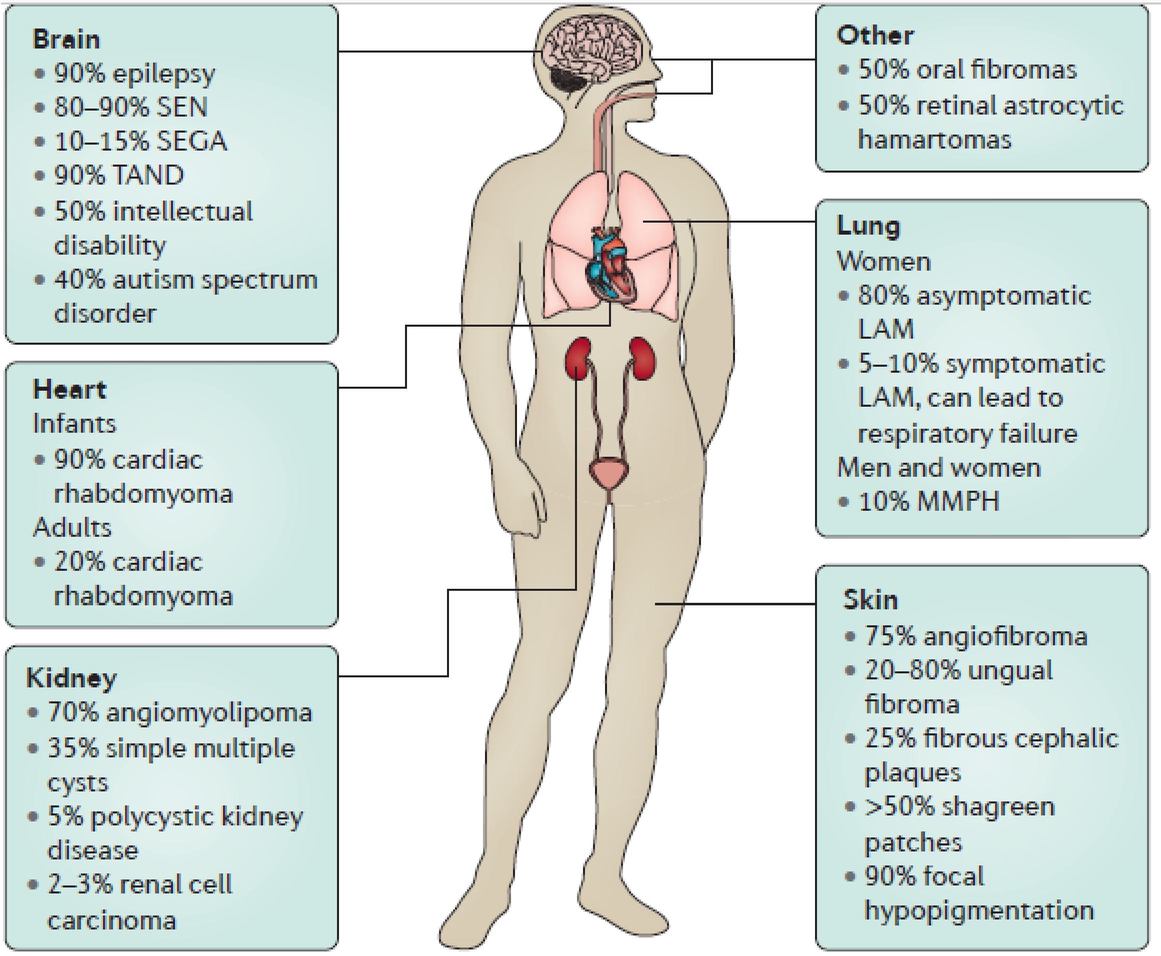

Brain
• 90% epilepsy
• 80–90% SEN
• 10–15% SEGA
• 90% TAND
• 50% intellectual disability
• 40% autism spectrum disorder
Heart
Infants
• 90% cardiac rhabdomyoma
Adults
• 20% cardiac rhabdomyoma
Kidney
• 70% angiomyolipoma
• 35% simple multiple cysts
• 5% polycystic kidney disease
• 2–3% renal cell carcinoma
Other
• 50% oral fibromas
• 50% retinal astrocytic hamartomas
Lung
Women
• 80% asymptomatic LAM
• 5–10% symptomatic LAM, can lead to respiratory failure
Men and women
• 10% MMPH
Skin
• 75% angiofibroma
• 20–80% ungual fibroma
• 25% fibrous cephalic plaques
• >50% shagreen patches
• 90% focal hypopigmentation

Figure 1 | **Clinical manifestations of TSC are diverse and affect multiple organs.** The most commonly affected systems and their associated lesions are shown. Percentages represent the approximate incidence in patients with tuberous sclerosis complex (TSC). LAM, lymphangioleiomyomatosis; MMPH, multifocal micronodular pneumocyte hyperplasia; SEGA, subependymal giant cell astrocytoma; SEN, subependymal nodule; TAND, tuberous sclerosis complex-associated neuropsychiatric disorder.

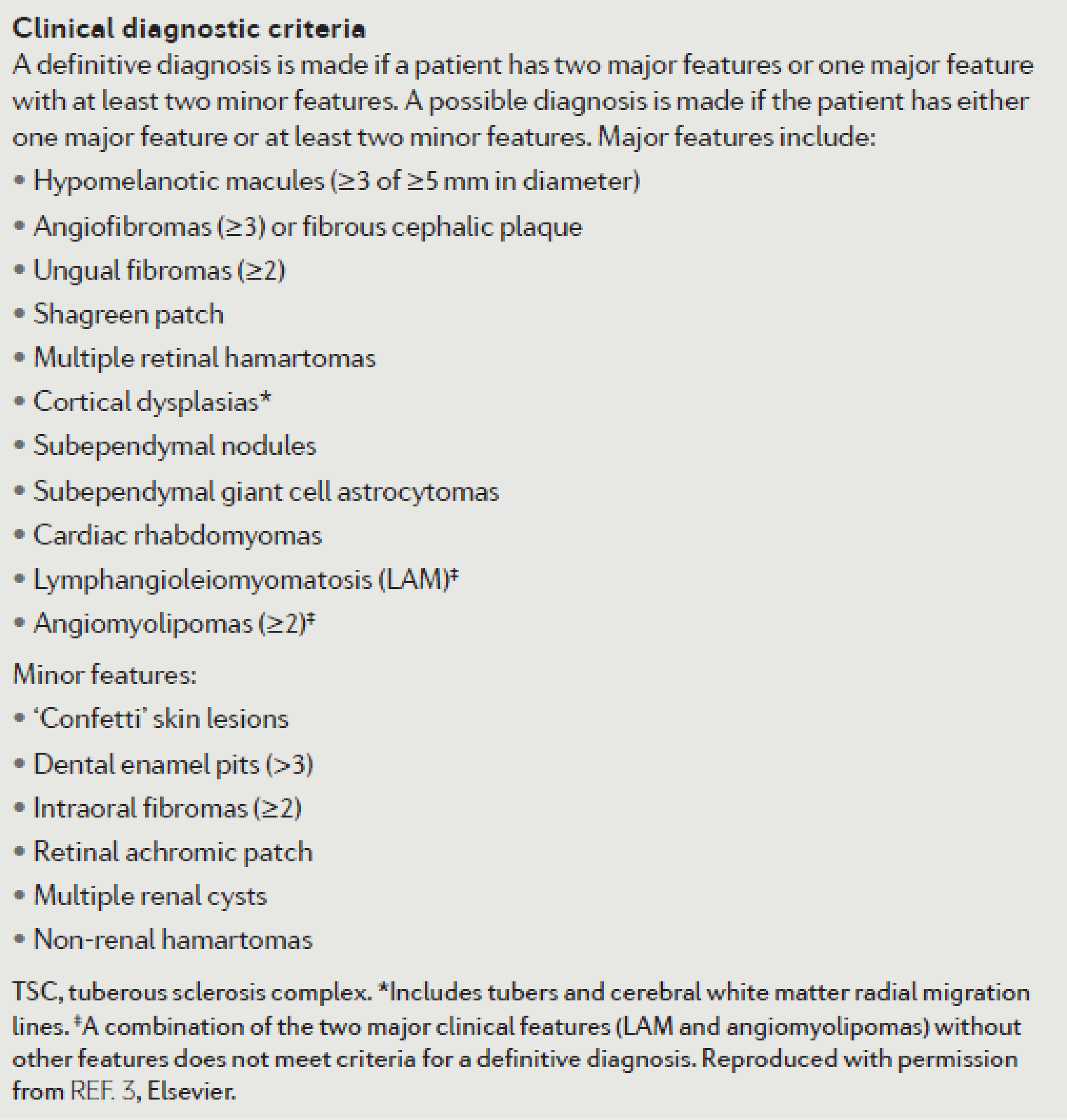
DIAGNOSTIC CRITERIA *(2012 updated criteria for TSC diagnosis)*

- *Genetic Criteria*
- *Clinical Criteria*

1.Genetic diagnostic criteria-

“The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definitive diagnosis of TSC. Approximately 10% of patients with TSC do not have a mutation that can be identified by conventional genetic testing, and a normal gene test result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

2. Clinical diagnostic criteria-



Clinical diagnostic criteria

A definitive diagnosis is made if a patient has two major features or one major feature with at least two minor features. A possible diagnosis is made if the patient has either one major feature or at least two minor features. Major features include:

- Hypomelanotic macules (≥3 of ≥5 mm in diameter)
- Angiofibromas (≥3) or fibrous cephalic plaque
- Ungual fibromas (≥2)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasias*
- Subependymal nodules
- Subependymal giant cell astrocytomas
- Cardiac rhabdomyomas
- Lymphangioleiomyomatosis (LAM)[‡]
- Angiomyolipomas (≥2)[‡]

Minor features:

- ‘Confetti’ skin lesions
- Dental enamel pits (>3)
- Intraoral fibromas (≥2)
- Retinal achromic patch
- Multiple renal cysts
- Non-renal hamartomas

TSC, tuberous sclerosis complex. *Includes tubers and cerebral white matter radial migration lines. [‡]A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definitive diagnosis. Reproduced with permission from REF. 3, Elsevier.

Management-

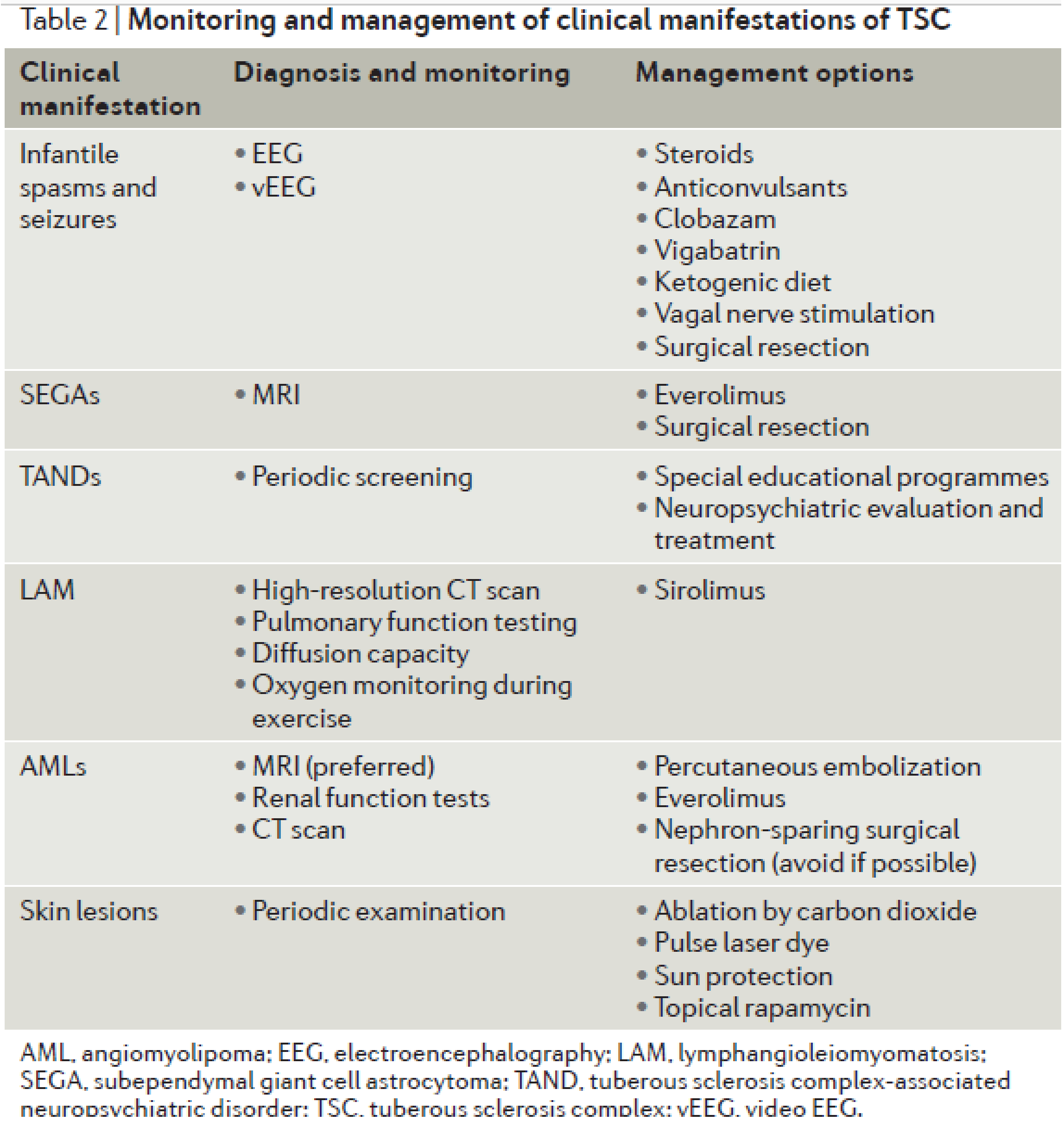


Table 2 | **Monitoring and management of clinical manifestations of TSC**

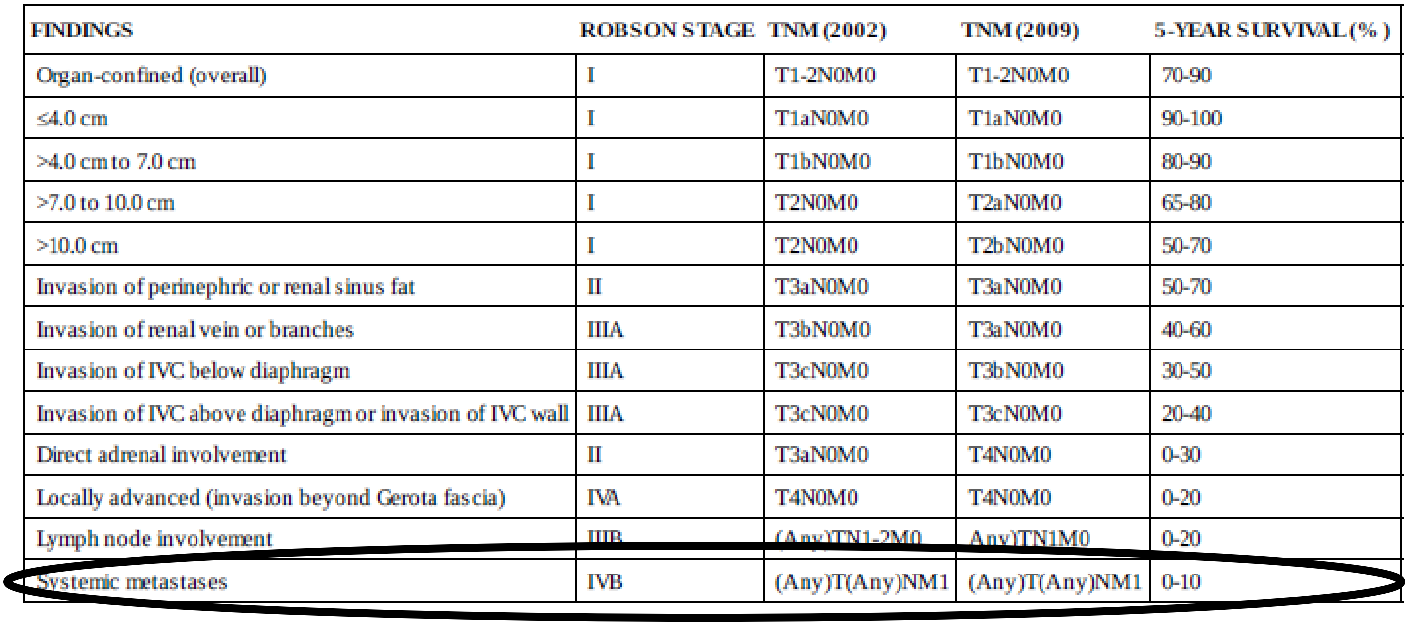
Clinical manifestation	Diagnosis and monitoring	Management options
Infantile spasms and seizures	• EEG • vEEG	• Steroids • Anticonvulsants • Clobazam • Vigabatrin • Ketogenic diet • Vagal nerve stimulation • Surgical resection
SEGAs	• MRI	• Everolimus • Surgical resection
TANDs	• Periodic screening	• Special educational programmes • Neuropsychiatric evaluation and treatment
LAM	• High-resolution CT scan • Pulmonary function testing • Diffusion capacity • Oxygen monitoring during exercise	• Sirolimus
AMLs	• MRI (preferred) • Renal function tests • CT scan	• Percutaneous embolization • Everolimus • Nephron-sparing surgical resection (avoid if possible)
Skin lesions	• Periodic examination	• Ablation by carbon dioxide • Pulse laser dye • Sun protection • Topical rapamycin

AML, angiomyolipoma; EEG, electroencephalography; LAM, lymphangioleiomyomatosis; SEGA, subependymal giant cell astrocytoma; TAND, tuberous sclerosis complex-associated neuropsychiatric disorder; TSC, tuberous sclerosis complex; vEEG, video EEG.

Metastatic RCC/ TKIs

One third of all RCC will present with metastases and one third will develop metastases after treatment of localized disease on follow-up

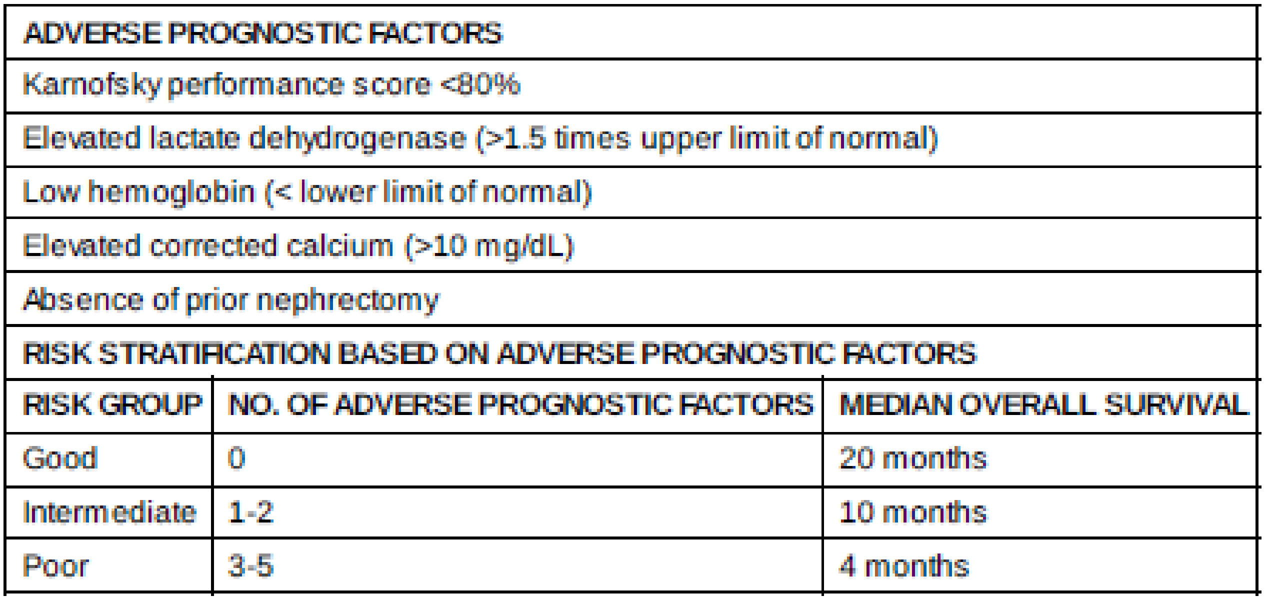
Survival



FINDINGS	ROBSON STAGE	TNM (2002)	TNM (2009)	5-YEAR SURVIVAL (%)
Organ-confined (overall)	I	T1-2N0M0	T1-2N0M0	70-90
≤4.0 cm	I	T1aN0M0	T1aN0M0	90-100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	80-90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	65-80
>10.0 cm	I	T2N0M0	T2bN0M0	50-70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	50-70
Invasion of renal vein or branches	IIIA	T3bN0M0	T3aN0M0	40-60
Invasion of IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	30-50
Invasion of IVC above diaphragm or invasion of IVC wall	IIIA	T3cN0M0	T3cN0M0	20-40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	0-30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	0-20
Lymph node involvement	IIIB	(Any)TN1-2M0	Any)TN1M0	0-20
Systemic metastases	IVB	(Any)T(Any)NM1	(Any)T(Any)NM1	0-10

Prognostic nomograms

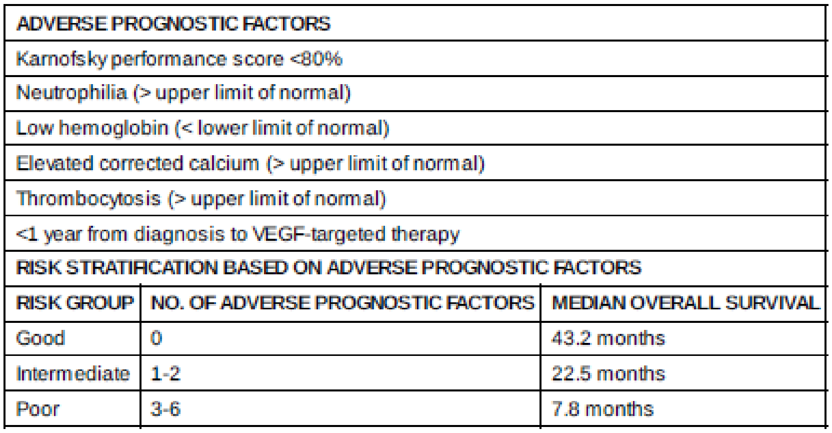
MSKCC/ Motzer criteria



ADVERSE PROGNOSTIC FACTORS
Karnofsky performance score <80%
Elevated lactate dehydrogenase (>1.5 times upper limit of normal)
Low hemoglobin (< lower limit of normal)
Elevated corrected calcium (>10 mg/dL)
Absence of prior nephrectomy

RISK STRATIFICATION BASED ON ADVERSE PROGNOSTIC FACTORS		
RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	20 months
Intermediate	1-2	10 months
Poor	3-5	4 months

IMDC/ Heng criteria (International Metastatic RCC Database Consortium)



ADVERSE PROGNOSTIC FACTORS		
Karnofsky performance score <80%		
Neutrophilia (> upper limit of normal)		
Low hemoglobin (< lower limit of normal)		
Elevated corrected calcium (> upper limit of normal)		
Thrombocytosis (> upper limit of normal)		
<1 year from diagnosis to VEGF-targeted therapy		
RISK STRATIFICATION BASED ON ADVERSE PROGNOSTIC FACTORS		
RISK GROUP	NO. OF ADVERSE PROGNOSTIC FACTORS	MEDIAN OVERALL SURVIVAL
Good	0	43.2 months
Intermediate	1-2	22.5 months
Poor	3-6	7.8 months

Cytoreductive nephrectomy followed by targeted therapy

Rationale

Nephrectomy has shown spontaneous regression of metastases in 1% patients

Patients who have a bulky primary do not respond well to targeted therapy- ? T cell inhibition

Only retrospective small studies for IL-2 and Sunitinib

Adjuvant IL-2 showed an 18% response rate with 20 month median OS

Adjuvant Sunitinib also showed a 10 month OS benefit after cytoreductive nephrectomy

Adjuvant IFN alpha in an RCT showed a a 3-10 month improvement in median OS vs no treatment

Metastatectomy

Favourable outcome only if good performance, oligometastatic disease that can be completely resected

Age <60 yrs, ECOG 0/1, >1 year disease free, solitary pulmonary metastasis < 4cm: Good outcome

Incomplete resection: 15 months vs 41 months median OS for complete resection of metastases

Local/ palliative therapy

Hypofractionated image guided RT (IGRT) 24 Gy to bone relieved symptoms and improved PFS

Currettage of lesion + fixation (impending fracture/ spine compression) showed similar results

RT improved symptoms in case of brain metastases

Palliative nephrectomy for intractable haematuria, pain. All above therapies only if performance status allows it.

Chemotherapy

Only in case of Sarcomatoid histology if performance status is good: Gemcitabine + Doxorubicin

Collecting duct: Gemcitabine + Carboplatin showed OS of 10 months

IFN alpha (18 MU s/c thrice weekly) and Bevacizumab (10 mg/kg IV every 2 weeks)

-In the metastatic setting, IFN showed an overall response rate of 13%, median OS of 8 months vs 6 months (Medroxyprogesterone Acetate) and 16 months vs 8 months (Vinblastine)- both significant

-Combination witb Bevacizumab showed an improved response rate upto 30% with a median PFS of 10 months vs 5 months (IFN alone). However, there was no OS benefit

-Bevacizumab: Hypertension, fatigue, bleeding and proteinuria

IL-2 (6-7.2 lakh units IV/ kg q8h for 5 days)

Response rate of 10-20% and median OS of 12-17 months

Very toxic: Vascular leak, hypotension, respiratory distress & 2-5% mortality. No added benefit with IFN

Sunitinib(400 mg OD)

Second line setting, cytokine refractory

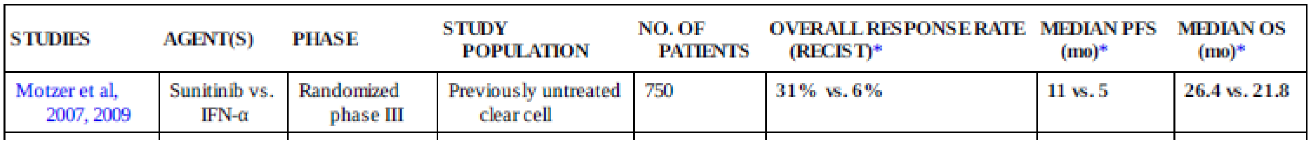
Response rate of 10% and median OS 18 vs 14 months (Placebo)- not significant

Side effects: Hypertension, fatigue, diarrhoea and hand foot syndrome

Sunitinib (50 mg OD for 4 weeks-2 weeks gap)

EFFECT trial: RCT vs IFN alpha

50 mg OD for 4 weeks followed by 2 weeks gap



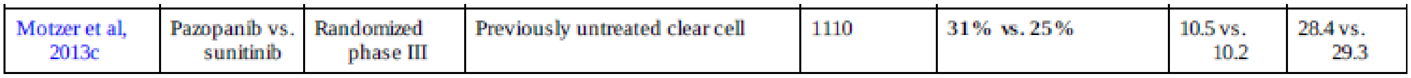
STUDIES	AGENT(S)	PHASE	STUDY POPULATION	NO. OF PATIENTS	OVERALL RESPONSE RATE (RECIST)*	MEDIAN PFS (mo)*	MEDIAN OS (mo)*
Motzer et al, 2007, 2009	Sunitinib vs. IFN-α	Randomized phase III	Previously untreated clear cell	750	31% vs. 6%	11 vs. 5	26.4 vs. 21.8

Multiple side effects: Hypertension, fatigue, diarrhoea, hand foot syndrome, pancytopenia, hypothyroidism

Thereby approved first line for metastatic clear cell RCC

Pazopanib (800 mg OD)

COMPARZ: Non-inferior to Sunitinib as first line for clear cell RCC



Motzer et al, 2013c	Pazopanib vs. sunitinib	Randomized phase III	Previously untreated clear cell	1110	31% vs. 25%	10.5 vs. 10.2	28.4 vs. 29.3

PISCES: 70% of patients preferred Pazopanib vs 22% who preferred Sunitinib due to better toxicity

All side effects of Sunitinib but milder, higher hepatotoxicity

Nivolumab (PD L1 inhibitor- 3 mg per kilogram of body weight, 60-minute IV every 2 weeks)

-**Checkmate 025**: Compared with Everolimus in an RCT, 2nd/3rd line, metastatic clear cell RCC

-Nivolumab has superior OS to everolimus ([HR]: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus. No PFS advantage.

-Fewer grade 3 or 4 toxicity events

-Approved second line for clear cell RCC

Cabozantinib(Met, VEGF and AXL inhibitor- 60 mg PO OD)

-**METEOR** trial: Cabozantinib vs everolimus RCT in VEGF resistant metastatic clear cell RCC

-The median PFS for cabozantinib was 7.4 vs. 3.8 months for everolimus- 42% improvement

-The median OS was 21.4 months with cabozantinib and 16.5 months with everolimus

- Grade 3 or 4 adverse events were reported in 74% with cabozantinib and 65% with everolimus.

-Approved 2nd line for clear cell RCC

Axitinib

-Inhibitors of VEGFR-1,2,3

-Benefit in patients who failed Sunitinib

- Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). No improvement in OS

-Diarrhoea, fatigue, hypertension

Temsirolimus (25 mg IV once a week)

- First line temsirolimus or IFN-α monotherapy, or a combination of both [362]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN-α group was not superior

-INTORSECT showed better PFS for Sunitninb vs Temsirolimus- Not recommended as first line

-ADR: Mucositis, fatigue, rash, hyperglycemia, dyslipidaemia

Everolimus (10 mg PO OD)

-RECORD 1: vs placebo. Better PFS (5 vs 1 month) for Everolimus. Similar OS in 2nd line setting

-RECORD 2: Bevacizumab + Everolimus vs Bevacizumab + IFN in 1st and 2nd line setting

-RECORD 3: Sequencing compared with Sunitinib. Sunitinib showed better PFS (11 vs 8 months) and OS (32 vs 22 months) when used as 1st line- Not recommended as 1st line

Non clear cell RCC

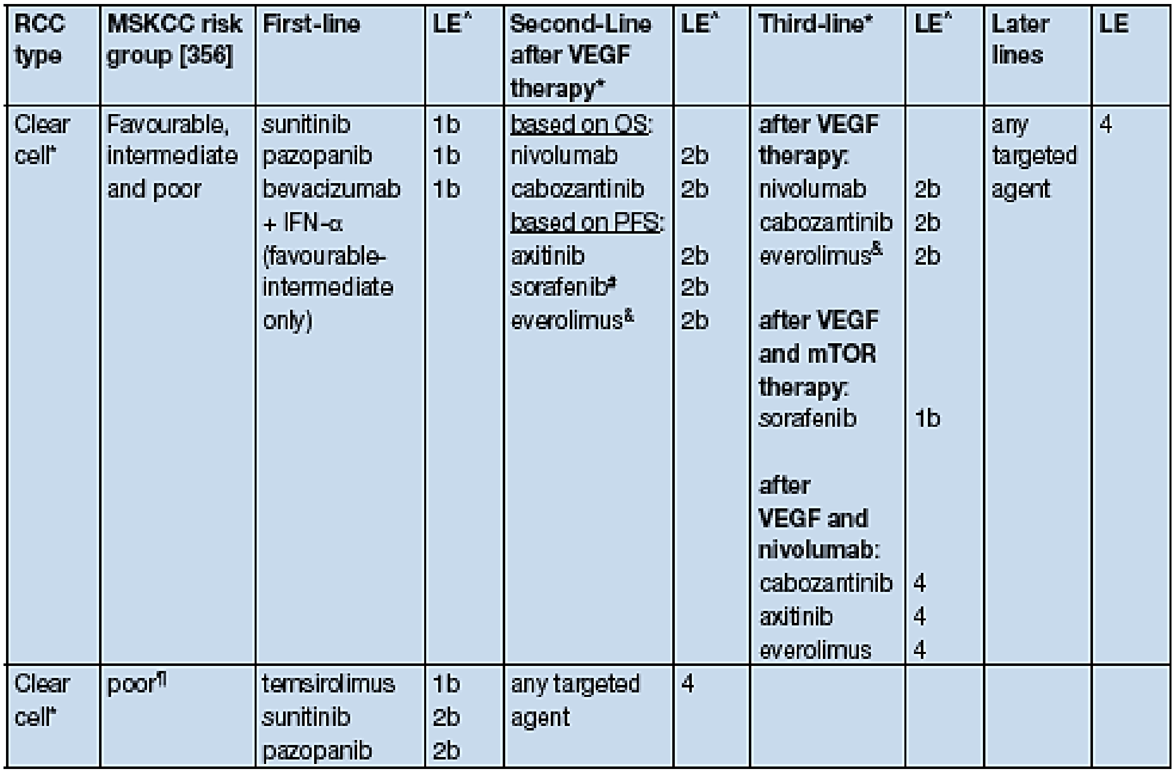
-No RCT, VEGR inhibitors only modest effect

-RAPTOR: Phase II, Everolimus. PFS of 4 months and OS of 21 months in papillary RCC

-HPRCC (Hereditary Papillary RCC)- MET (7p31). Foretinib (Acts against MET and VEGFR-2)- 240 mg days 1-5 every 14 days or 80 mg OD: PFS of 9 months. Hogh response in the presence of proven MET mutation

-HLRCC (Hereditary Leiomyomatosis and RCC)- Fumarate hydratase (1q42): Bevacizumab + Erlotinib: 10 months PFS

Summary



RCC type	MSKCC risk group [356]	First-line	LE^	Second-Line after VEGF therapy*	LE^	Third-line*	LE^	Later lines	LE
Clear cell*	Favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN-α (favourable-intermediate only)	1b 1b 1b	based on OS: nivolumab cabozantinib based on PFS: axitinib sorafenib# everolimus&	 2b 2b 2b 2b 2b	**after VEGF therapy:** nivolumab cabozantinib everolimus& **after VEGF and mTOR therapy:** sorafenib **after VEGF and nivolumab:** cabozantinib axitinib everolimus	 2b 2b 2b 1b 4 4 4	any targeted agent	4
Clear cell*	poor¶	temsirolimus sunitinib pazopanib	1b 2b 2b	any targeted agent	4				

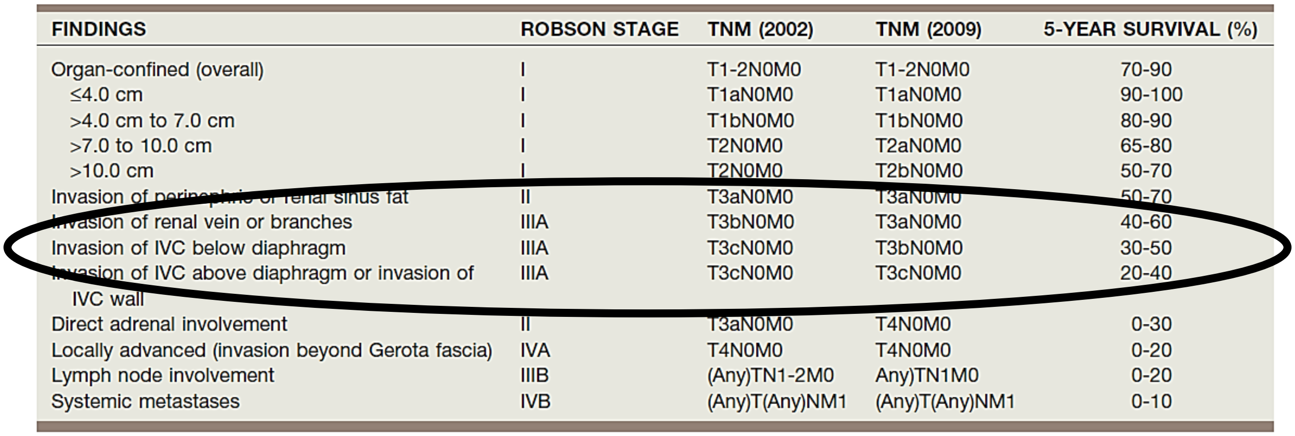
Non clear cell: Any TKI

RCC with IVC thrombus

Involvement of the venous system with RCC occurs in 4% to 10%

45-70% can be cured with aggressive surgery

Suspected in patients with a renal tumor who also have
- -lower extremity edema,
- -isolated right-sided varicocele or varicocoele does not collapse with recumbency
- -dilated superficial abdominal veins
- -proteinuria,
- -pulmonary embolism/ right atrial mass

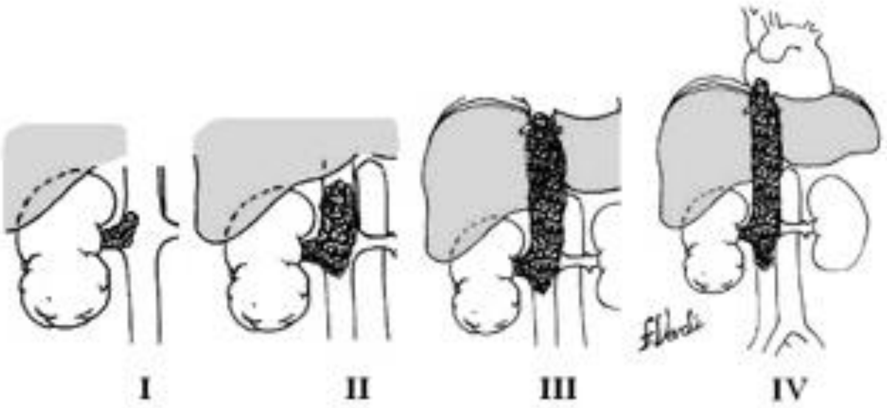


FINDINGS	ROBSON STAGE	TNM (2002)	TNM (2009)	5-YEAR SURVIVAL (%)
Organ-confined (overall)	I	T1-2N0M0	T1-2N0M0	70-90
≤4.0 cm	I	T1aN0M0	T1aN0M0	90-100
>4.0 cm to 7.0 cm	I	T1bN0M0	T1bN0M0	80-90
>7.0 to 10.0 cm	I	T2N0M0	T2aN0M0	65-80
>10.0 cm	I	T2N0M0	T2bN0M0	50-70
Invasion of perinephric or renal sinus fat	II	T3aN0M0	T3aN0M0	50-70
Invasion of renal vein or branches	IIIA	T3bN0M0	T3aN0M0	40-60
Invasion of IVC below diaphragm	IIIA	T3cN0M0	T3bN0M0	30-50
Invasion of IVC above diaphragm or invasion of IVC wall	IIIA	T3cN0M0	T3cN0M0	20-40
Direct adrenal involvement	II	T3aN0M0	T4N0M0	0-30
Locally advanced (invasion beyond Gerota fascia)	IVA	T4N0M0	T4N0M0	0-20
Lymph node involvement	IIIB	(Any)TN1-2M0	Any)TN1M0	0-20
Systemic metastases	IVB	(Any)T(Any)NM1	(Any)T(Any)NM1	0-10

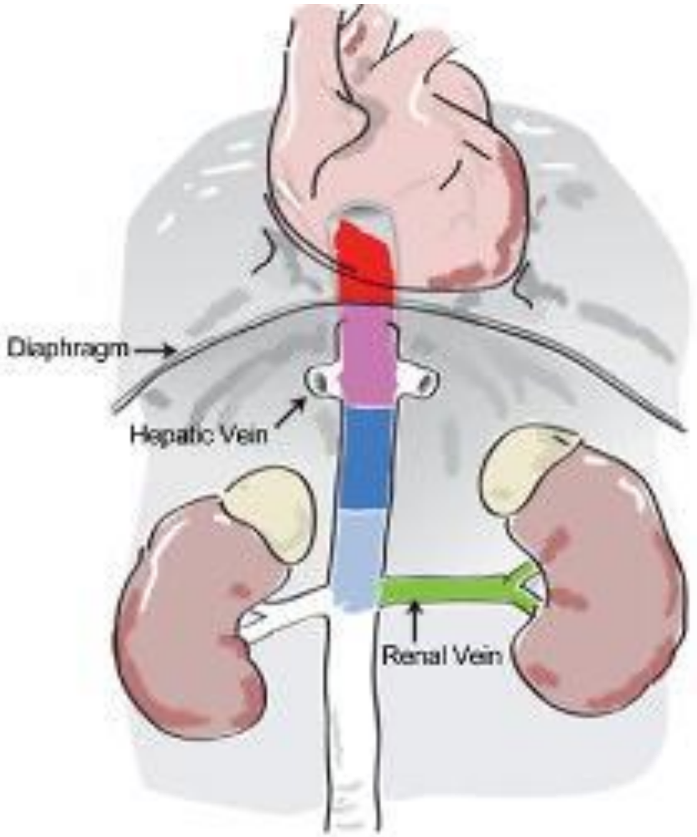
Investigations
Blood: CBC, creatinine, LFT, LDH, ESR, Ca/P
Urine routine
Cystoscopy
CECT thorax, abdomen + pelvis with delayed films or MRI
MRI: Slightly better delineation of IVC wall invasion and bland/ tumour thrombus. Needs Gadolinum
Others: Angiography, trans-oesophageal echo

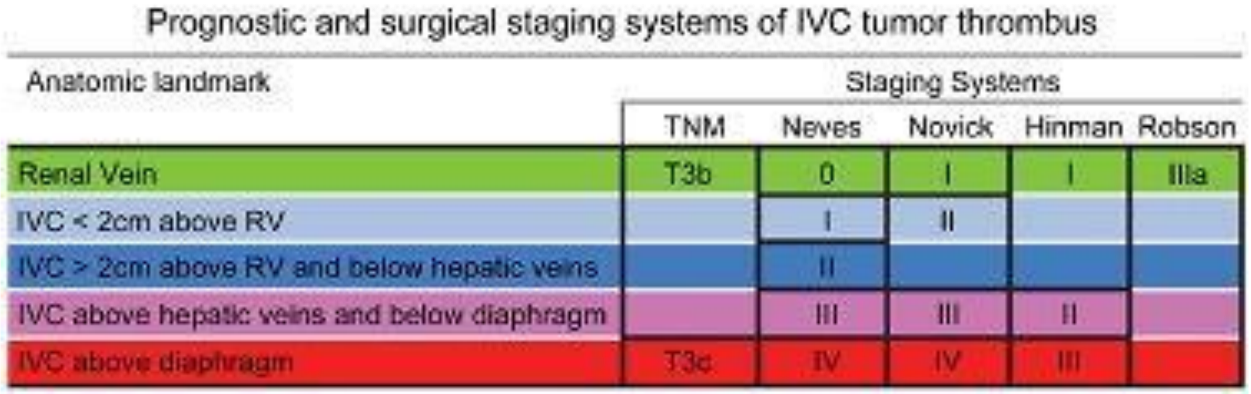
Classification

Neves- Zincke



Ciancio modification of Neves and Zincke (level III and IV)
IIIa; Subhepatic
IIIb: Intrahepatic
IIIc: Suprahepatic, infradiaphragmatic
IV: Supradiaphragmatic
Summary of classification systems




Prognostic and surgical staging systems of IVC tumor thrombus

Anatomic landmark	Staging Systems				
	TNM	Neves	Novick	Hinman	Robson
Renal Vein	T3b	0	I	I	IIIa
IVC < 2cm above RV		I	II		
IVC > 2cm above RV and below hepatic veins		II			
IVC above hepatic veins and below diaphragm		III	III	II	
IVC above diaphragm	T3c	IV	IV	III	

Management principle

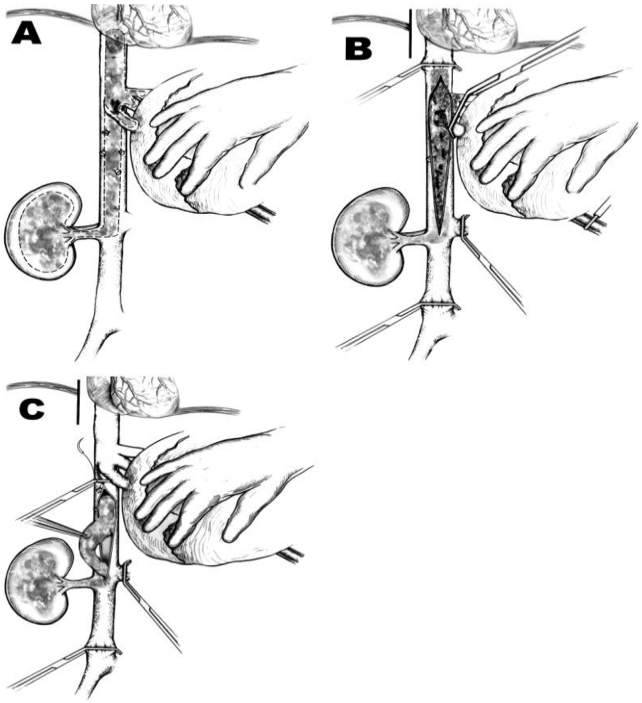
Thrombus level	**MRI**	**Cephalad control**	**Venovenous/ cardiopulmonary bypass**
I	Subhepatic	May need caudate mobilization	No
II	Intrahepatic	Liver mobilization, Pringle's	No
III	Supra-diaphragmatic/ atrial thrombus	Sternotomy/ transdiaphragmatic / Ciancio	May be needed

Clamping sequence

Below—opposite renal vein—above thrombus.
Release in the same order

Ciancio technique

-GA, arterial + central lines + epidural, SCDs, supine, Chevron or full midline, Omnitract
-Transdiaphragmatic thrombus removal
-Laparotomy, medial colonic mobilization along the White line of Toldt
-Kocherization of duodenum, identification of IVC and dissection of anterior wall of IVC
-Identification of left renal vein. Right renal artery may be tied in the interaortocaval groove
-Liver mobilization after division of Falciform, coronary, right and left triangular ligaments
-Division of tributaries from caudate to IVC to complete exposure of intra-abdominal IVC
-Dissection of diaphragmatic hiatus to free IVC, enlargement of hiatus to expose pericardium
-Open pericardium, identify right atrium and thrombus using TEE and clamp RA above thrombus
-Clamp veins in the sequence mentioned + Pringle. Milk thrombus into infrahepatic IVC
-Venotomy and extraction of thrombus. Venovenous bypass may be used (Between infrarenal IVC and IJV/ subclavian vein)
If IVC is infiltrated: Excise. Graft with PTFE/ dacron/ femoral vein/ GSV if insufficient collaterals



Cardiopulmonary bypass under deep hypothermic arrest

-Traditionally for supradiaphragmatic thrombi.
-Peri-operative mortality 15%
-Stroke 6.1%, coagulopathy- 25%
-May be circumvented with transdiaphragmatic approach under TEE monitoring:
-4.5% peri-operative mortality with Ciancio technique

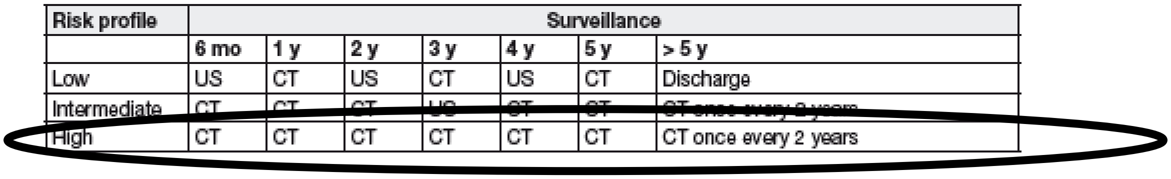
Hilar control (In general, not IVC thrombus)

-Ligate first and cut next vs cut first (between clamps) and ligate next
-Difficult to identify right renal artery: Interaortocaval groove, deep to left renal vein
-Difficult to identify left renal artery: Divide peritoneum between IMV and aorta and trace anterior surface of aorta proximally till left renal artery is palpated deep to ligament of Treitz
-Other options: Mass clamping with pedicle clamp and divide, hook out renal artery deep to left renal vein: Interaortocaval groove- right, para-aortic- left, pre-op embolization and vein first

Complications

-Bleeding, pulmonary/ air embolism, peri-op MI/ stroke, need for ventilation/ inotropes, hypothermia, coagulopathy and acidosis
-Atelectasis, wound infection, hernia
-Narrowing of IVC >50% circumference= Venous stasis and DVT, progressive worsening of renal function, recurrence- local/ distant

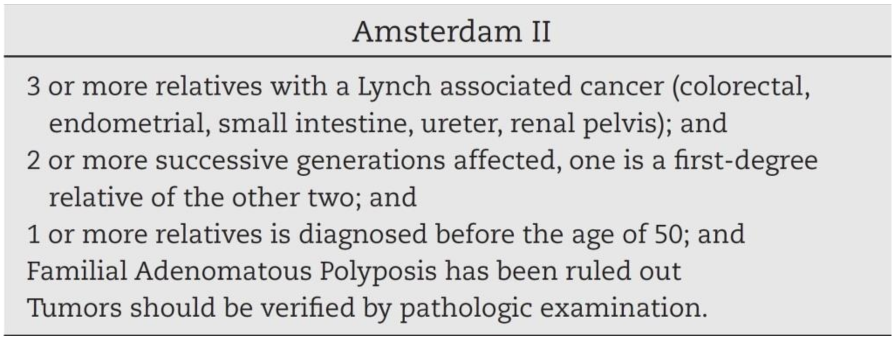
Follow-up



Risk profile	**Surveillance**						
	6 mo	**1 y**	**2 y**	**3 y**	**4 y**	**5 y**	**> 5 y**
Low	US	CT	US	CT	US	CT	Discharge
Intermediate	CT	CT	CT	US	CT	CT	CT once every 2 years
High	CT	CT	CT	CT	CT	CT	CT once every 2 years

UTUC

-5-10% of urothelial CA.
-Pyelocaliceal tumours are twice as common as ureteral tumours
-Ureter: 70% distal, 25% mid and 5% proximal (? Downstream implantation)
-17% of cases, concurrent bladder cancer present. Bilateral in 3-5% (Upto 25% if CIS bladder present)
-Bladder recurrence: 15-75%, contralateral recurrence: 2-6%. UTUC: 2-4% after bladder cancer
-60% invasive, 20% metastatic at diagnosis
-70-80 yrs, men 3 times more affected
-10-20% hereditary- <60 yrs, personal history of Lynch spectrum cancer or:



Amsterdam II

3 or more relatives with a Lynch associated cancer (colorectal, endometrial, small intestine, ureter, renal pelvis); and
2 or more successive generations affected, one is a first-degree relative of the other two; and
1 or more relatives is diagnosed before the age of 50; and
Familial Adenomatous Polyposis has been ruled out
Tumors should be verified by pathologic examination.

Risk factors

-Smoking: N hydroxylamine (RR- 2 for 20 and 6 for 60 pack years. Ureter> pelvis)
-Aromatic amines: Petroleum, dye, rubber work (beta naphthylamine, benzidine)
-Aristolochic acid: Balkan and chinese herb, p53 mutation (Bulky, multifocal/ bilateral, low grade)
-Arsenic exposure (Taiwan- Blackfoot disease. Ureter>pelvis)
-Urinary stones/ chronic infection
-Cyclophosphamide (Acrolein metabolite)
-Prior bladder cancer
-Laxatives>1 yr

Histology
75% urothelial
25% squamous, glandular, micropapillary, neuroendocrine (worse prognosis)

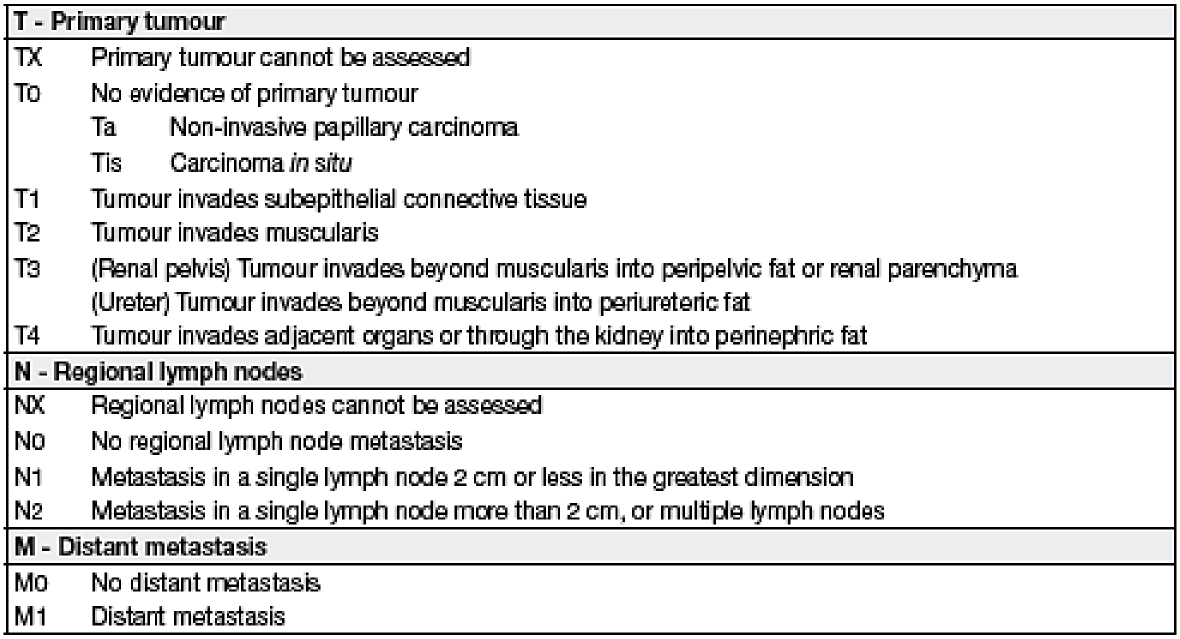
Clinical presentation
Haematuria 60-100%
Flank pain 30%- Tumour/ clot
Mass 20%
Weight loss, loss of appetite, fever, metastatic symptoms
Asymptomatic 15%

Investigations
CBC, creatinine, LFT, Ca/P, ESR, LDH, urine routine and culture
Cytology: Sensitivity 20% (grade 1), 45% (grade 2), 75% (grade 3)
CT urography: 100% sensitive, 60% specific
Urothelial cancer 46 HU vs uric acid calculi 100 HU average attenuation
Mass, filling defect, HUN (80% invasive), stranding
Adjacent organs, opposite kidney
MRI if renal failure. 75% sensitive for <2 cm tumours
Cystoscopy to rule out concomitant bladder pathology

Ureteroscopic biopsy: 85-90 % sensitive, 80-90% correlation with final biopsy (If conservation planned)
Brush biopsy: 90% sensitive and specific

Others: CT thorax, bone scan

Staging

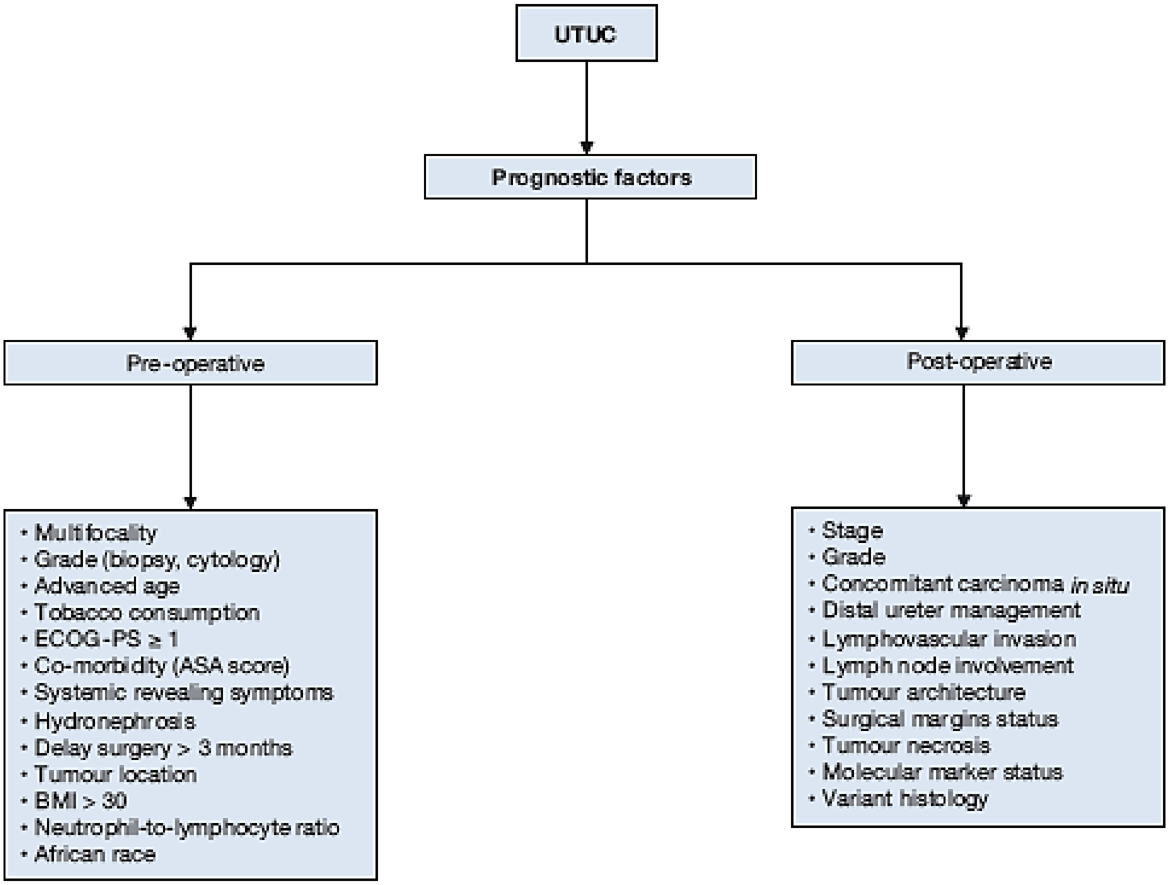


T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma
	(Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Stage	5 yr
0: TisN0M0	90
1: T1N0M0	70
2: T2N0M0	50
3: T3N0M0	25
4: T4/ N1/M1	0-5

90% of pelvic and 60% of ureteric tumours are high grade
CIS seen in 60-90% with renal pelvic tumours

Prognostic factors


UTUC
Prognostic factors
Pre-operative
Post-operative
• Multifocality
• Grade (biopsy, cytology)
• Advanced age
• Tobacco consumption
• ECOG-PS ≥ 1
• Co-morbidity (ASA score)
• Systemic revealing symptoms
• Hydronephrosis
• Delay surgery > 3 months
• Tumour location
• BMI > 30
• Neutrophil-to-lymphocyte ratio
• African race
• Stage
• Grade
• Concomitant carcinoma *in situ*
• Distal ureter management
• Lymphovascular invasion
• Lymph node involvement
• Tumour architecture
• Surgical margins status
• Tumour necrosis
• Molecular marker status
• Variant histology

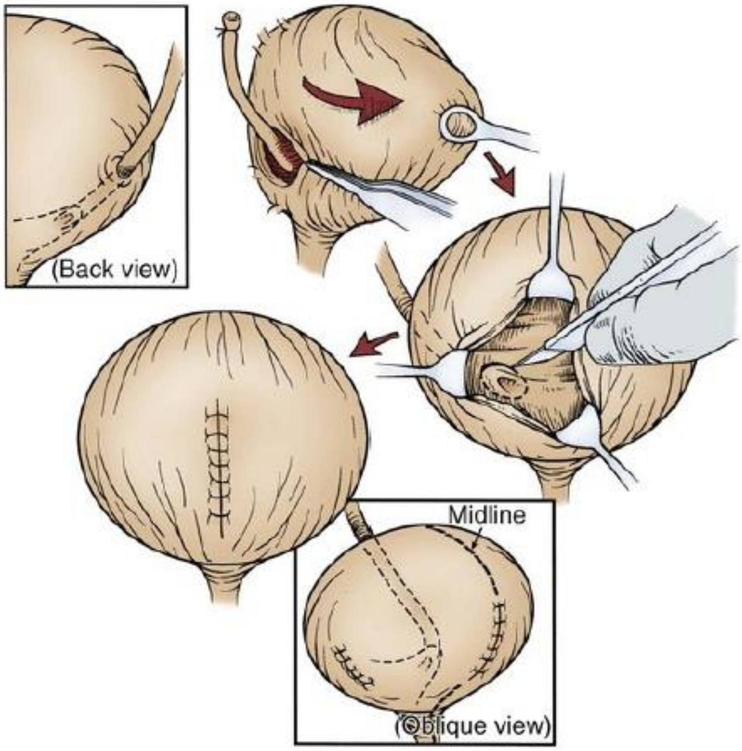
P53 overexpression, MSI
Others: p27, Bcl-2, HIF 1 alpha. EGFR, NF kB, c-MET, aneuploidy

Prediction tools

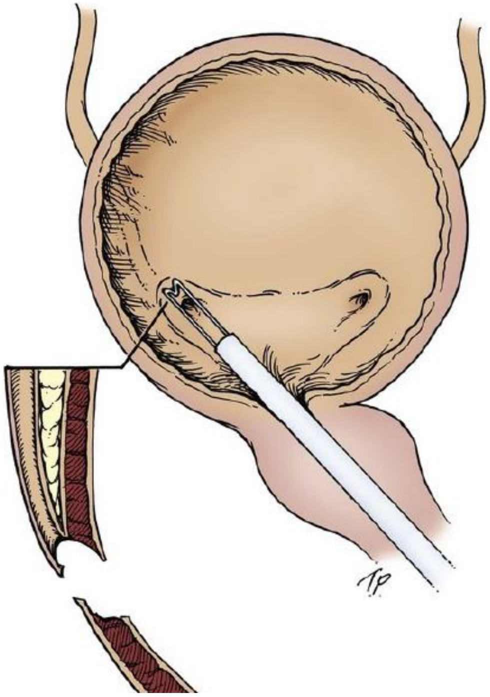
Margulis (pre-op): Location, appearance and grade- non-organ confined disease (77% accurate)
Post-op nomograms: Jeldres, Yates, Cha and Roupret (Age, stage, grade, location, LVI, sessile, CIS)
Increased accuracy- 80%

Treatment
Ablative
Lap or open RNU with bladder cuff gold standard
Techniques for addressing distal ureter:

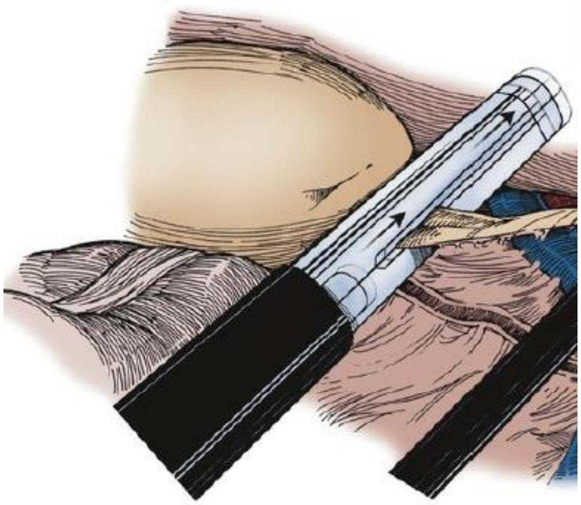
1. Open cuff: Transvesical, extravesical or combined



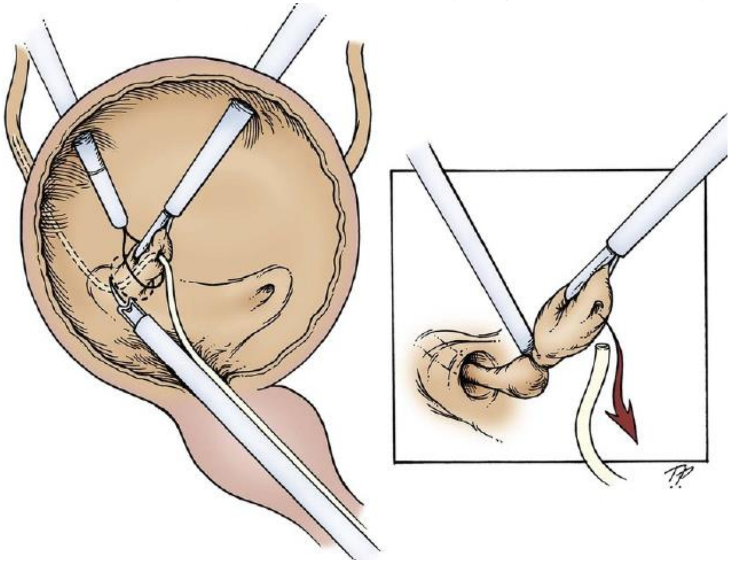
2. Abercrobie’s snatch or pluck technique



3. Total laparoscopic: Mobilize till VUJ and fire a stapler across. Risk of leaving intramural ureter



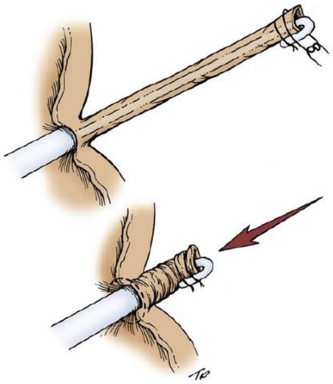
4. Transvesical ligation and detachment: Ureteric catheter placed, Colling's knife to cut till fat around ureteric orifice, endoloop vis transvesical laparoscopic ports (5 mm X2) placed around lower ureter and cinched before proceeding to NU. No spillage but technically demanding



5. Stripping/ intussusception

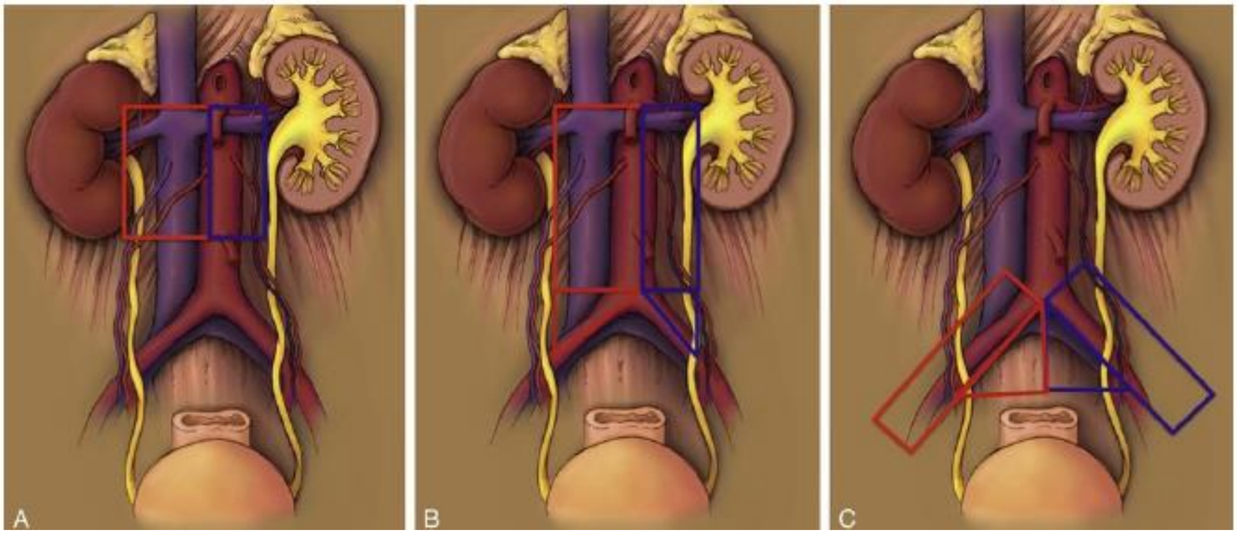
Not to be used for ureteric tumours. Least preferred due to opening of the ureter

Ureteric orifice placed pre-op, ureter divided after NU, ureteric catheter tied to distal segment and then extracted transvesically by incising around UO with Colling's and everting the ureter into the bladder with traction on the ureteric catheter



Lymphadenectomy

12-25% have N+ disease
8 or more nodes
Few case series reported better survival with lymphadenectomy, evidence lacking
Pelvic: Right: Hilar, para,pre and retrocaval + inter-aortocaval upto IMA. Left: Hilar, para-aortic till IMA
Upper 2/3 of ureter extend template till ureteric crossing. Lower ureter: EI, II, O, presacral



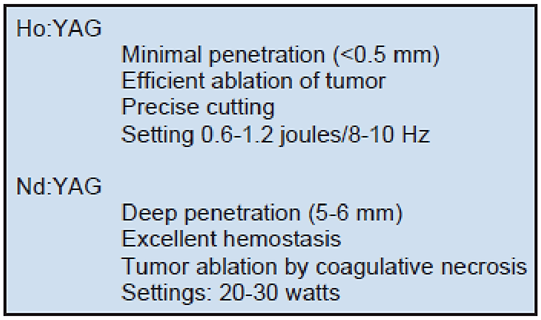
Post-op intravesical MMC before CBD removal produces an absolute reduction in risk of bladder recurrence of 11%, a relative reduction of 40%. Number needed to treat to prevent one bladder tumour is nine (ODMIT C).

Segmental ureterectomy/ distal ureterectomy with 1 cm margin followed by uretero-ureterostomy or uretero-neocystostomy in solitary kidney, elderly, renal function compromise or incomplete endoscopic resection of low grade solitary tumour- 50% 2 yr survival, 33-55% recurrence ipsilateral.

Endoscopic management

Solitary kidney/ bilateral disease/ renal failure
Solitary, low grade, low volume that can be completely resected
Ureteroscopy: 55% bladder recurrence, 25% ureteric recurrence, 30% overall mortality in 2-8 yrs
15% risk of stricture, recurrence, nephrectomy
Resect/ snare + fulgurate base/ ablate with laser

Percutaneous: 35% ureter and 25% bladder recurrence. 20% mortality in 2-6 yrs
20% nephrectomy and 15% progression rate
For bulky/ lower pole tumours
Resect/ cold cup + fulgurate base/ ablate with laser
Nephrostomy: Relook, staged resection, instillation of BCG or MMC


Ho:YAG
Minimal penetration (<0.5 mm)
Efficient ablation of tumor
Precise cutting
Setting 0.6-1.2 joules/8-10 Hz

Nd:YAG
Deep penetration (5-6 mm)
Excellent hemostasis
Tumor ablation by coagulative necrosis
Settings: 20-30 watts

Close surveillance needed

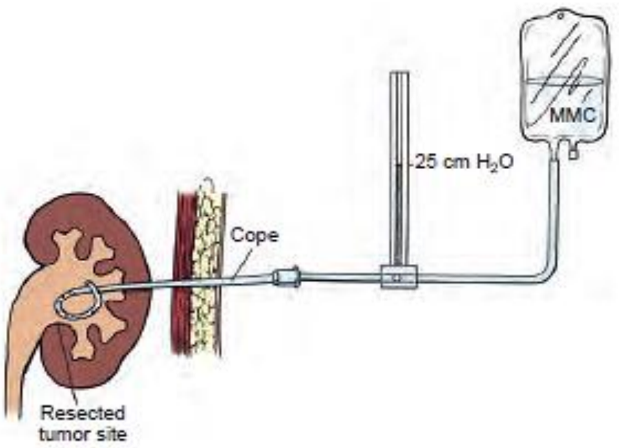
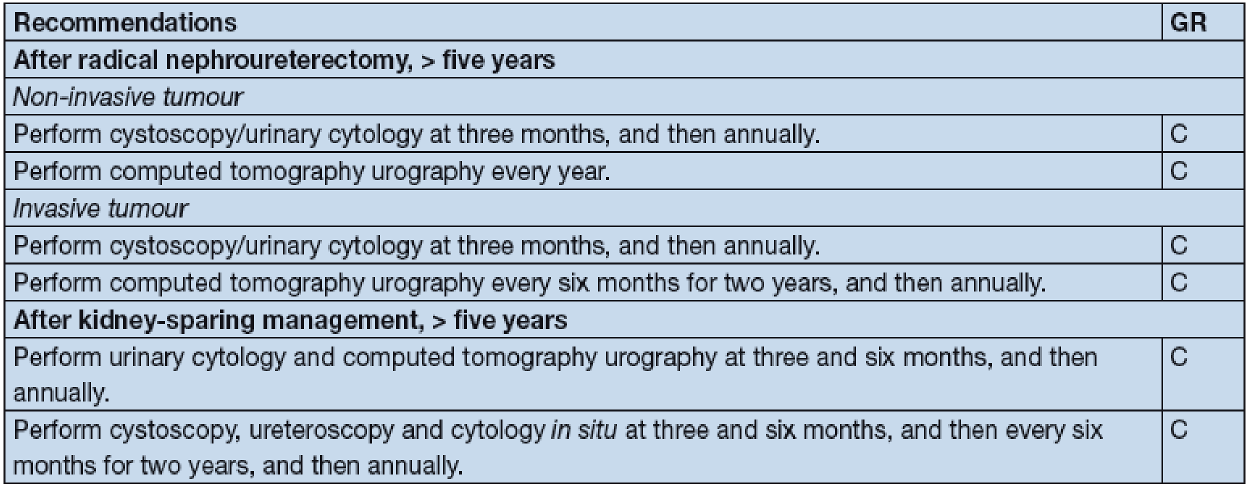


Figure 58-35. **Setup for administration of topical immunotherapy or chemotherapy to the upper urinary tract through a previously placed nephrostomy tube. Therapy is instilled by gravity with a mechanism that prevents excessive intrarenal pressures. High pressures have been linked to complications of systemic absorption and bacterial sepsis. MMC, mitomycin C.**

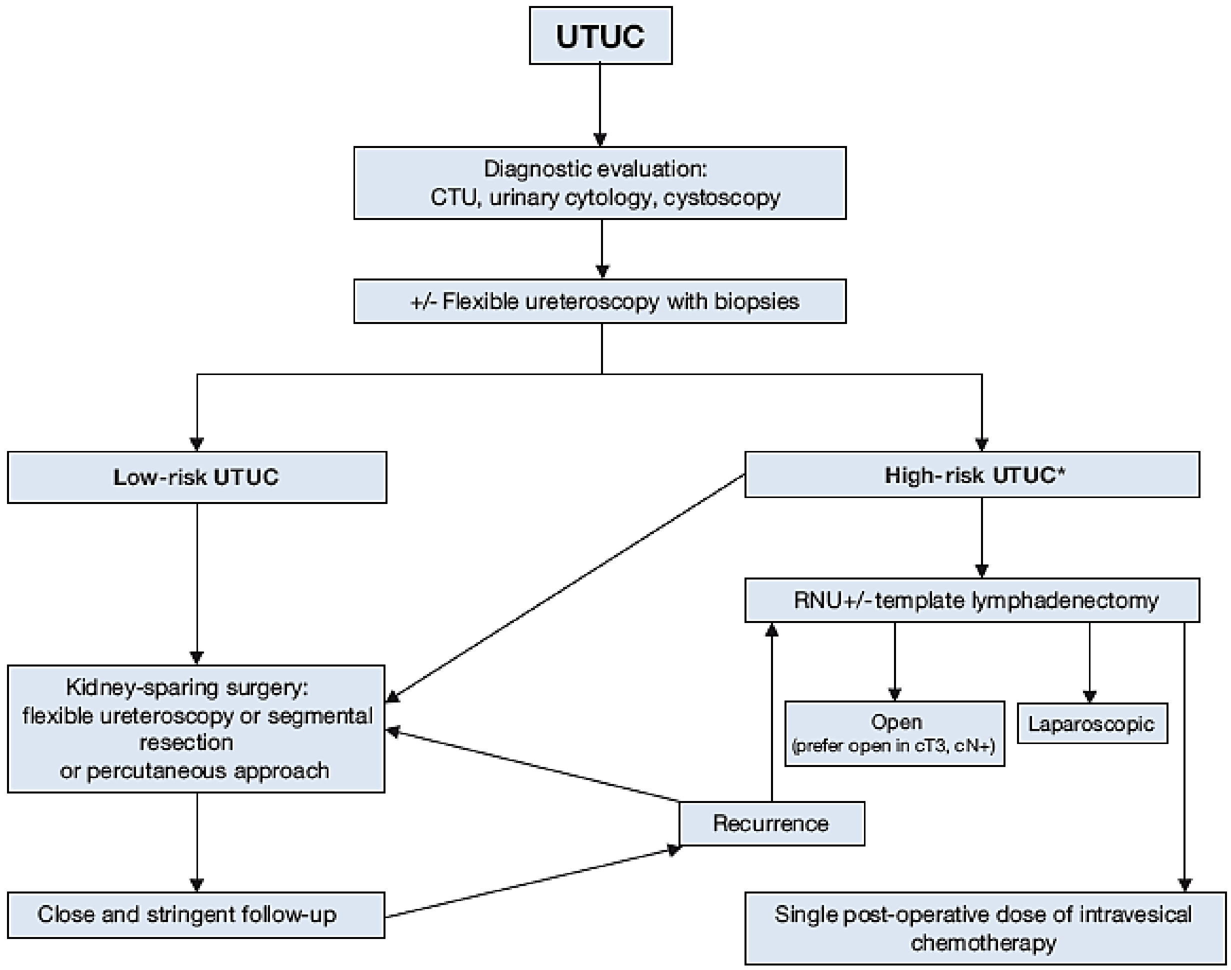
BCG: 240-360 mg in 500 ml NS over 2 hours once weekly for 6 weeks.

Follow-up

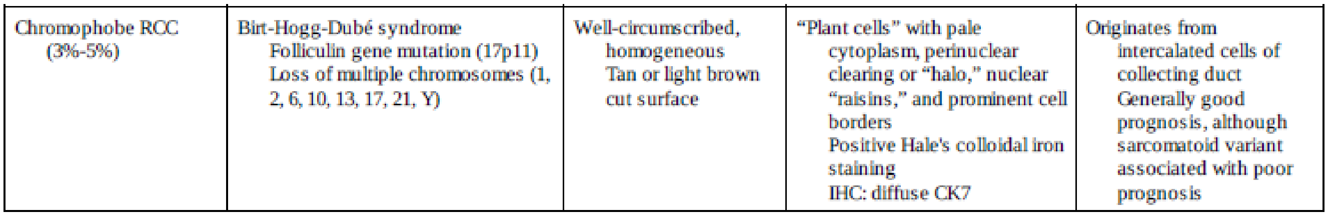


Recommendations	**GR**
After radical nephroureterectomy, > five years	
Non-invasive tumour	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every year.	C
Invasive tumour	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every six months for two years, and then annually.	C
After kidney-sparing management, > five years	
Perform urinary cytology and computed tomography urography at three and six months, and then annually.	C
Perform cystoscopy, ureteroscopy and cytology *in situ* at three and six months, and then every six months for two years, and then annually.	C

Summary


UTUC
Diagnostic evaluation:
CTU, urinary cytology, cystoscopy
+/- Flexible ureteroscopy with biopsies
Low-risk UTUC
High-risk UTUC*
RNU+/-template lymphadenectomy
Open
(prefer open in cT3, cN+)
Laparoscopic
Kidney-sparing surgery:
flexible ureteroscopy or segmental resection
or percutaneous approach
Recurrence
Close and stringent follow-up
Single post-operative dose of intravesical chemotherapy

Chromophobe RCC



Chromophobe RCC (3%-5%)	Birt-Hogg-Dubé syndrome Folliculin gene mutation (17p11) Loss of multiple chromosomes (1, 2, 6, 10, 13, 17, 21, Y)	Well-circumscribed, homogeneous Tan or light brown cut surface	"Plant cells" with pale cytoplasm, perinuclear clearing or "halo," nuclear "raisins," and prominent cell borders Positive Hale's colloidal iron staining IHC: diffuse CK7	Originates from intercalated cells of collecting duct Generally good prognosis, although sarcomatoid variant associated with poor prognosis

Also seen in SDH mutations
Fuhrman cannot be used as there is significant nuclear atypia
Sunitinib/ Pazopanib for metastatic tumours

Upper tract malignancy

VHL

Hereditary autosomal dominant syndrome associated with RCC

Due to mutations in VHL tumour suppressor gene on chromosome 3p25-26 (Two hit)

VHL is a protein that binds to Hypoxia Inducible Factor (HIF-2α) and causes its Ubiquitin mediated degradation

Mutation/ methylation/ deletion leads to deactivation of VHL

Mutated VHL is either unable to bind to Elongin or HIF which leads to unchecked activation of HIF (Analogous to a hypoxic state- HIF 1 and 2 dimerize to translocate to the nucleus)

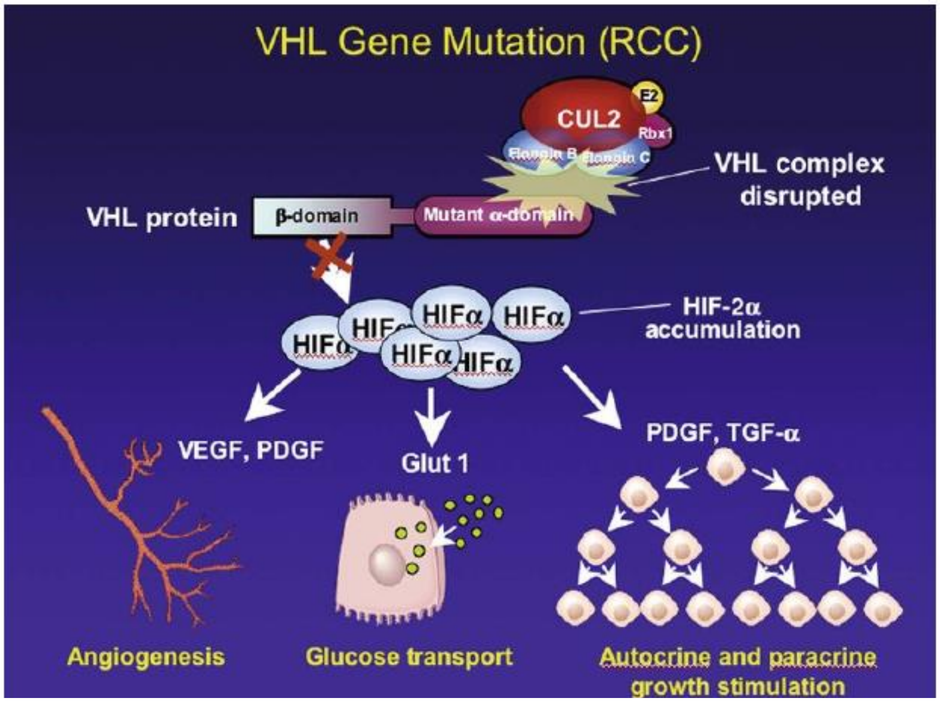
This produces over-expression of:

-VEGF: Neovascularization and growth of tumour

-PDGF: Stabilization of pericytes around new blood vessels contributing to angiogenesis

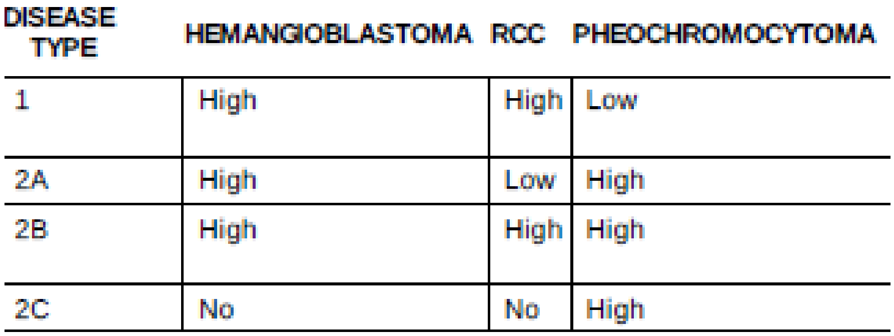
-GLUT 1: Increased glucose transport into tumour

-TGF α: Growth



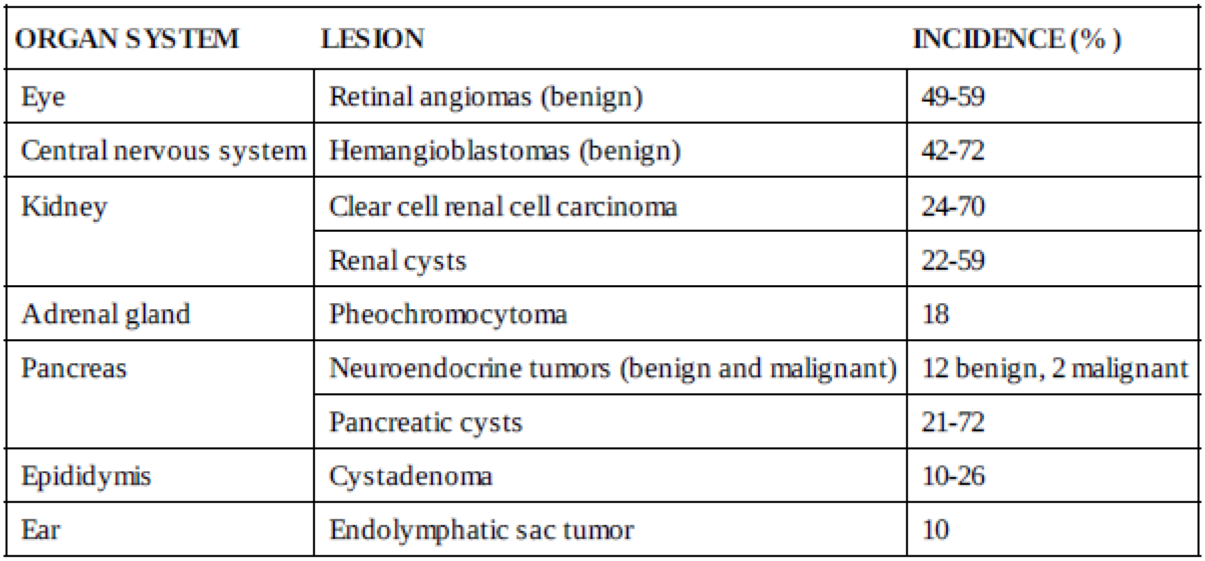
VHL has been found to be mutated in 90% of sporadic clear cell RCC as well

Types:



DISEASE TYPE	HEMANGIOBLASTOMA	RCC	PHEOCHROMOCYTOMA
1	High	High	Low
2A	High	Low	High
2B	High	High	High
2C	No	No	High

Manifestations:



ORGAN SYSTEM	LESION	INCIDENCE (%)
Eye	Retinal angiomas (benign)	49-59
Central nervous system	Hemangioblastomas (benign)	42-72
Kidney	Clear cell renal cell carcinoma	24-70
	Renal cysts	22-59
Adrenal gland	Pheochromocytoma	18
Pancreas	Neuroendocrine tumors (benign and malignant)	12 benign, 2 malignant
	Pancreatic cysts	21-72
Epididymis	Cystadenoma	10-26
Ear	Endolymphatic sac tumor	10

Most common: Retinal angiomas (50-60%)- Start by 2 yrs age and impair vision if untreated

5% of phaeochromocytomas are malignant in VHL.

High incidence of multiple/ bilateral RCC + phaeochromocytoma: nephron/ adrenal sparing Sx

Screening schedule:

Organ	Screening test	Frequency/ age
-	VHL mutation	1st year
Eye	Fundoscopy	Annual from 2nd year
Brain/ spine	MRI	Annual from 16 years
Abdomen	USG (child)/ MRI (older child)	Annual from 8 years
Ear	Tympanometry	Every 2/3 yrs from 2 yrs age

Annual abdominal, neurological, epididymal examination

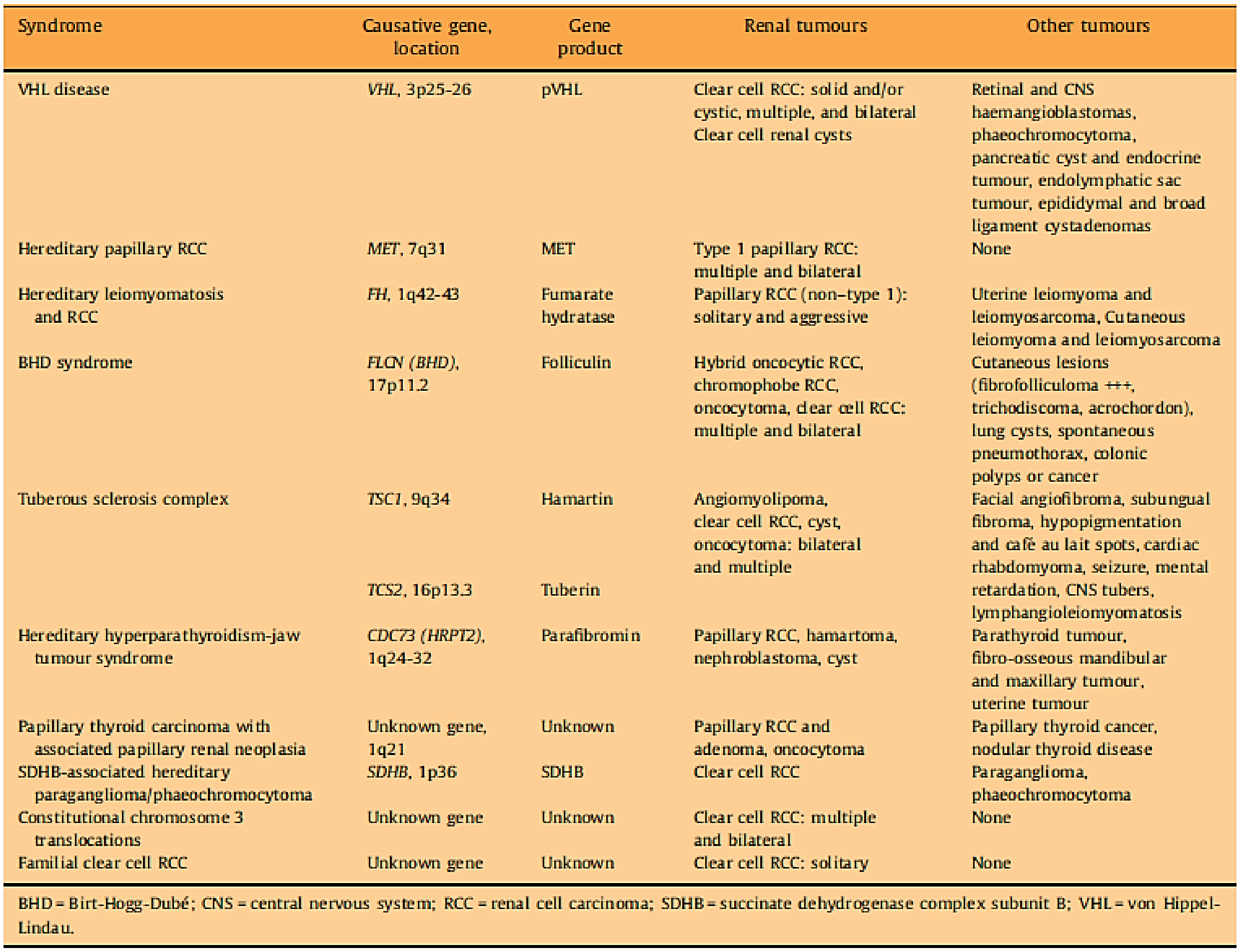
Hereditary and familial RCC

3-5% of all RCC, at least 12 known syndromes

Median age at diagnosis is 37 years

Characterized by multiple, bilateral disease of early onset.

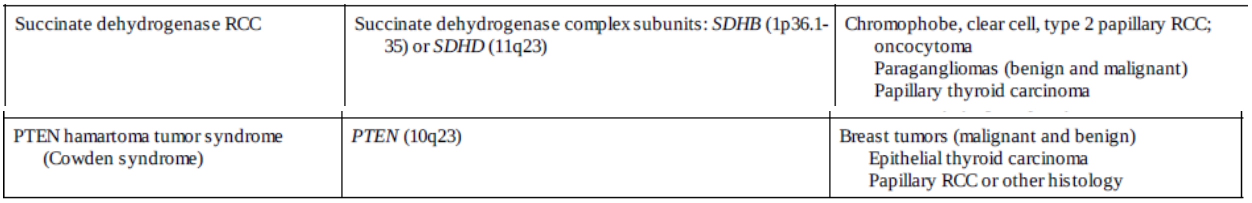
NSS in all at 3 cm tumour size except HLRCC and SDH related RCC



Syndrome	Causative gene, location	Gene product	Renal tumours	Other tumours
VHL disease	*VHL*, 3p25-26	pVHL	Clear cell RCC: solid and/or cystic, multiple, and bilateral Clear cell renal cysts	Retinal and CNS haemangioblastomas, phaeochromocytoma, pancreatic cyst and endocrine tumour, endolymphatic sac tumour, epididymal and broad ligament cystadenomas
Hereditary papillary RCC	*MET*, 7q31	MET	Type 1 papillary RCC: multiple and bilateral	None
Hereditary leiomyomatosis and RCC	*FH*, 1q42-43	Fumarate hydratase	Papillary RCC (non–type 1): solitary and aggressive	Uterine leiomyoma and leiomyosarcoma, Cutaneous leiomyoma and leiomyosarcoma
BHD syndrome	*FLCN (BHD)*, 17p11.2	Folliculin	Hybrid oncocytic RCC, chromophobe RCC, oncocytoma, clear cell RCC: multiple and bilateral	Cutaneous lesions (fibrofolliculoma +++, trichodiscoma, acrochordon), lung cysts, spontaneous pneumothorax, colonic polyps or cancer
Tuberous sclerosis complex	*TSC1*, 9q34	Hamartin	Angiomyolipoma, clear cell RCC, cyst, oncocytoma: bilateral and multiple	Facial angiofibroma, subungual fibroma, hypopigmentation and café au lait spots, cardiac rhabdomyoma, seizure, mental retardation, CNS tubers, lymphangioleiomyomatosis
	TCS2, 16p13.3	Tuberin		
Hereditary hyperparathyroidism-jaw tumour syndrome	*CDC73 (HRPT2)*, 1q24-32	Parafibromin	Papillary RCC, hamartoma, nephroblastoma, cyst	Parathyroid tumour, fibro-osseous mandibular and maxillary tumour, uterine tumour
Papillary thyroid carcinoma with associated papillary renal neoplasia	Unknown gene, 1q21	Unknown	Papillary RCC and adenoma, oncocytoma	Papillary thyroid cancer, nodular thyroid disease
SDHB-associated hereditary paraganglioma/phaeochromocytoma	*SDHB*, 1p36	SDHB	Clear cell RCC	Paraganglioma, phaeochromocytoma
Constitutional chromosome 3 translocations	Unknown gene	Unknown	Clear cell RCC: multiple and bilateral	None
Familial clear cell RCC	Unknown gene	Unknown	Clear cell RCC: solitary	None

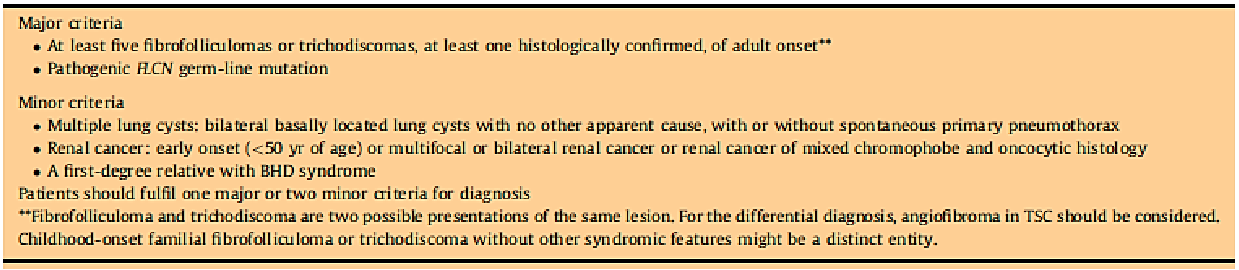
BHD = Birt-Hogg-Dubé; CNS = central nervous system; RCC = renal cell carcinoma; SDHB = succinate dehydrogenase complex subunit B; VHL = von Hippel-Lindau.

Verine J et al. European Urology 2010



Succinate dehydrogenase RCC	Succinate dehydrogenase complex subunits: *SDHB* (1p36.1-35) or *SDHD* (11q23)	Chromophobe, clear cell, type 2 papillary RCC; oncocytoma Paragangliomas (benign and malignant) Papillary thyroid carcinoma
PTEN hamartoma tumor syndrome (Cowden syndrome)	*PTEN* (10q23)	Breast tumors (malignant and benign) Epithelial thyroid carcinoma Papillary RCC or other histology

Diagnostic criteria for Birt Hogg Dube syndrome



Major criteria
- At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset**
- Pathogenic *FLCN* germ-line mutation

Minor criteria
- Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
- Renal cancer: early onset (<50 yr of age) or multifocal or bilateral renal cancer or renal cancer of mixed chromophobe and oncocytic histology
- A first-degree relative with BHD syndrome

Patients should fulfil one major or two minor criteria for diagnosis

**Fibrofolliculoma and trichodiscoma are two possible presentations of the same lesion. For the differential diagnosis, angiofibroma in TSC should be considered. Childhood-onset familial fibrofolliculoma or trichodiscoma without other syndromic features might be a distinct entity.

Screening and cancer risk (AUA update 2015, National Cancer Institute guidelines)

Syndrome	Risk of RCC	Screening starts at
VHL	20-70%	8 years
HPRCC	Almost 100%	21 years
Birt Hogg Dube	30%	21 years
HLRCC	30%	10 years
TSC	1-4%	?
Hyperparathyroidism jaw tumour	Up to 15%	?

The rest: Surveillance could be started at 30–35 yr of age and/or 10 yr before the earliest age of onset of an RCC in a given family.

Familial RCC: Two or more family members with RCC but no syndromic association

Refer for genetic testing if:

-Known mutation in family member (VHL, HPRCC, HLRCC, BHD, SDH, TS)
-Non clear cell with unusual histology (Oncocytoma, hybrid, chromophobe)
-Bilateral/ multifocal
-<45 years RCC
-First or second degree relative affected
-Pneumothorax/ fibrofolliculomas/ seizure disorder/ lymphangioleiomyomatosis/ phaeo+PGL/multiple fibroids <30 yrs/skin leiomyomas/ retinal or cerebellar or brain stem or spinal cord haemagioblastomas

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Multidrug resistance in RCC

Multiple mechanisms suggested:

-Overexpression of cell membrane efflux pumps: MDR-1 P-gp *and* MRP-1
-Deficient activation of CD 95 mediated apoptosis
-Up-regulation of Glutathione S trasnferase isoforms mu and theta (GSTM and GSTT) inhibits apoptosis
-Expression of energy dependant drug efflux pump P-Glycoprotein

Mechanisms specific for targeted therapy include:
-Activation of alternate pro-angiogenic proteins include FGF and IL-8
-Up-regulation of HIF in response to VEGF binding by Bevacizumab
-Compensatory increased expression of downstream effectors in mTOR pathway such as AKT

Biopsy in renal mass

Indications
-Indeterminate renal mass on imaging
-Patient planned for active surveillance
-Patient planned for ablative therapy
-Extensive metastases not amenable to surgical therapy- To confirm diagnosis before TKIs

Contraindications
When watchful waiting is planned in view of poor performance status of patient
Uncontrolled coagulopathy
Predominantly cystic, small renal masses

Technique

-CT or ultrasound guidance

-Patient should be off anticoagulation for at least 5 days.

-Infiltration of lignocaine 2% along biopsy tract as decided on imaging

-18 G core biopsy needle, 2 cores from solid component of tumour (4 cores if >10 cm/ T2b)

-Coaxial needle- decreased seeding

-Yield is high if >4 cm, peripheral, solid and poor for <4 cm, cystic, necrotic, centrally located tumours

-IHC (E.g. CaIX, Vimentin, Cytokeratin-7, AMACR) may be used to augment positive yield of biopsy.

Complications

<1%: Bleeding, pneumothorax, haemothorax. Needle tract seeding is exceedingly rare

Results

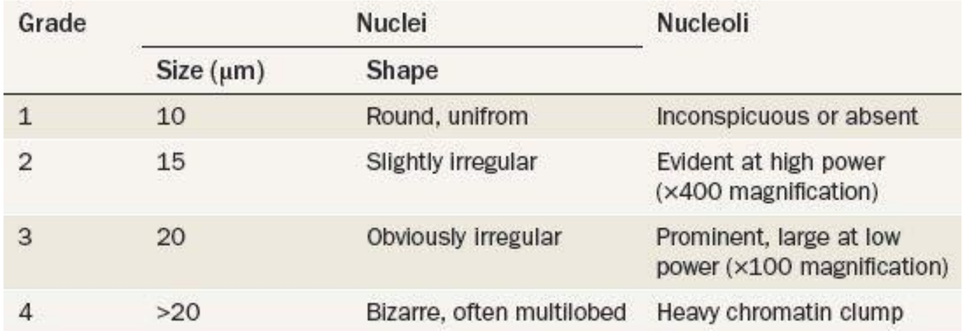
Sensitivity and specificity are 99%

8% of masses may show indeterminate biopsy- repeat biopsy is diagnostic in 83-100%

Correlation with final histopathology is about 90%

False negative rates <5% in referral centres

Fuhrman and ISUP grading



Grade	Nuclei		Nucleoli
	Size (μm)	Shape	
1	10	Round, unifrom	Inconspicuous or absent
2	15	Slightly irregular	Evident at high power (×400 magnification)
3	20	Obviously irregular	Prominent, large at low power (×100 magnification)
4	>20	Bizarre, often multilobed	Heavy chromatin clump

Fuhrman grading (One 100X or 400X field showing maximum pleomorphism is chosen)

Susan Fuhrman, Pathologist, Ohio- As a part of residency dissertation, 1982

Strengths

-Used in clear and papillary RCC. Chromophobe has intrinsic nuclear atypia and Fuhrman should not be used.

-Part of several prognostic nomograms (SSIGN, Karakiewicz, UISS)

-Accuracy >80% in multicentre validation for survival

Drawbacks

-Ssignificant inter-observer variability with only slight correlation between observers (Kappa value 0.22).

-Two-tiered model (1,2-low and 3,4-high), it was equally valid with less variability (Kappa value 0.44)

-There is very little difference in survival between grade 2 and 3.

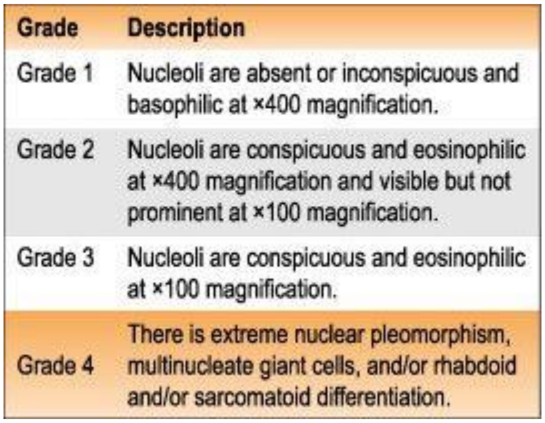
-Mixed histology, loss to follow-up and non-standard management were flaws in the original series.

-The three criteria do not go hand in hand. If discordant, it is not known which criteria takes precedence.

-Size and shape were mostly non-contributory to prognostication

Kappa
0.0 Poor
.20 Slight
.40 Fair
.60 Moderate
.80 Substantial
1.0 Almost perfect

ISUP (International Society of Urological Pathology) grading-2012



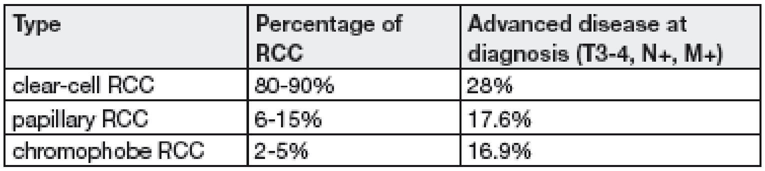
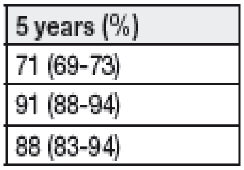
Grade	Description
Grade 1	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification.
Grade 2	Nucleoli are conspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification.
Grade 3	Nucleoli are conspicuous and eosinophilic at ×100 magnification.
Grade 4	There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

-Nucleolar prominence is more objective with good inter-observer agreement
-Better correlation with survival in few retrospective series
-Has replaced Fuhrman grading for RCC
-Prospective validation studies lacking at present

Prognostic factors in RCC
May be classified as anatomical, pathological, clinical and molecular

Anatomical factors that worsen prognosis
Size
Higher stage
Invasion of perinephric fat/ adjacent organs
Lymph node involvement
Metastases

Adverse pathological features
-Clear cell/ sarcomatoid

Type	Percentage of RCC	Advanced disease at diagnosis (T3-4, N+, M+)	5 years (%)
clear-cell RCC	80-90%	28%	71 (69-73)
papillary RCC	6-15%	17.6%	91 (88-94)
chromophobe RCC	2-5%	16.9%	88 (83-94)

-Type 2 papillary RCC> type 1 papillary RCC
-Necrosis
-Lymphovascular invasion
-Grade (please expand from previous question)

Clinical adverse prognostic factors

- -Older age
- -Poor performance status
- -Symptomatic at presentation
- -Cachexia
- -Anaemia
- -Hypercalcaemia
- -Thrombocytosis
- -Neutrophilia
- -Increased Neutrophil-Lymphocyte ratio
- -Hypoalbuminaemia
- -Increased CRP

Molecular markers of adverse outcome

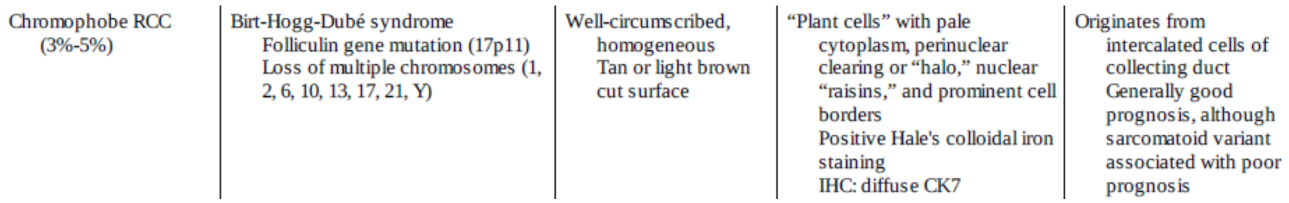
- -P53, p27 mutation
- -Ki-67 over expression
- -VEGF, HIF, PDGF, FGF over expression
- -BAP1 (BRCA Associated Protein 1) compared to PBRM 1 (Polybromo 1) mutation has worse prognosis
- -Single nucleotide polymorphisms, gene hypermethylation and microRNA abnormalities

(CAIX over expression predicts better response to IL-2 therapy)

Nomograms predicting survival (SSIGN alone, predicts recurrence)

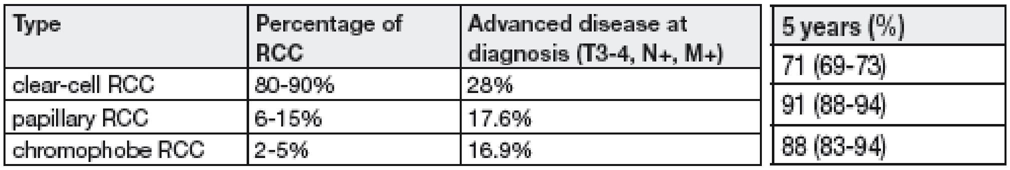
Name	Components	Accuracy
Pre-op		
Kanao	TNM	70%
Kutikov	Race, gender, age, size	70%
Post-op, localized		
SSIGN	Stage, size, grade, necrosis	80%
UISS	Stage, grade, ECOG	70%
Karakiewicz	Stage, size, grade, symptoms	85%
Metastatic		
MSKCC/ Motzer	Nephrectomy, Hb, Ca, LDH, Karnofsky	70%
IMDC/ Heng	Interval from diagnosis to TKI, Hb, Ca, Neutrophil, Platelet, Karnofsky	70%

Chromophobe RCC



Chromophobe RCC (3%-5%)	Birt-Hogg-Dubé syndrome Folliculin gene mutation (17p11) Loss of multiple chromosomes (1, 2, 6, 10, 13, 17, 21, Y)	Well-circumscribed, homogeneous Tan or light brown cut surface	"Plant cells" with pale cytoplasm, perinuclear clearing or "halo," nuclear "raisins," and prominent cell borders Positive Hale's colloidal iron staining IHC: diffuse CK7	Originates from intercalated cells of collecting duct Generally good prognosis, although sarcomatoid variant associated with poor prognosis

-Perinuclear halo/ clearing due to microvesicles containing mucopolysaccharide
-Also seen in SDH mutation. IHC: CK-7 (66% positive), Parvalbumin (100% positive)
-Inherent nuclear pleomorphism precludes Fuhrman grading
-Oncocytoma-Hybrid oncocytoma-Chromophobe RCC may be a continuum



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chromophobe RCC	2-5%	16.9%	88 (83-94)

HIFU

High intensity focused ultrasound is an experimental technique in ablation of renal tumours
Non-invasive, transcutaneous delivery (3500 W/cm2), 0.8–3.2 MHz under real time monitoring
This causes tissue to absorb energy-heat-cavitation and microbubble formation
Technical impediments: Respiratory movement, bowel/ rib interference- lap obviates this
Long treatment times (>5 hours), 10% show skin burns, viable tumour in up to 50% of patients who underwent post HIFU resection in some studies

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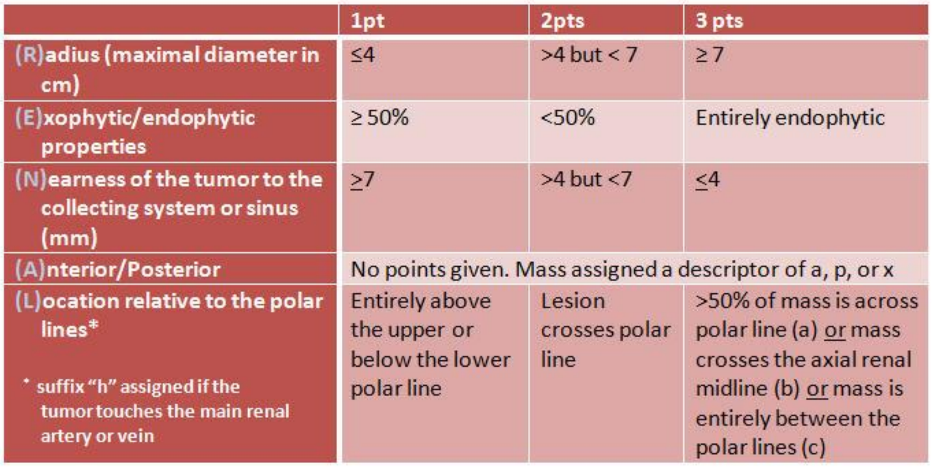
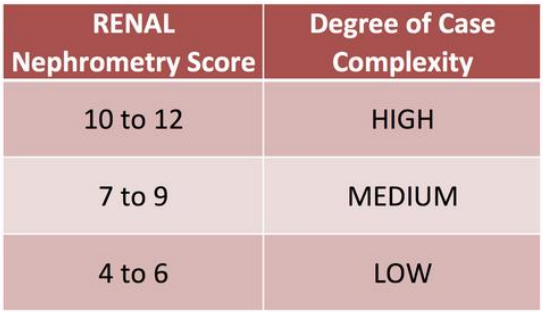
RENAL score

-Kutikov and Uzo
-Complexity of renal mass lesion based on size, endophytic component polar location, distance from collecting system and anterior/ posterior location

Components

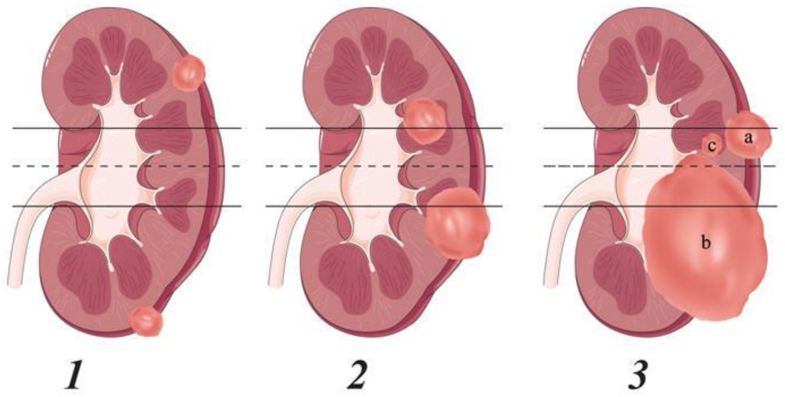


	1pt	2pts	3 pts
(R)adius (maximal diameter in cm)	≤4	>4 but < 7	≥ 7
(E)xophytic/endophytic properties	≥ 50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/Posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* * suffix "h" assigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)



RENAL Nephrometry Score	Degree of Case Complexity
10 to 12	HIGH
7 to 9	MEDIUM
4 to 6	LOW

L component

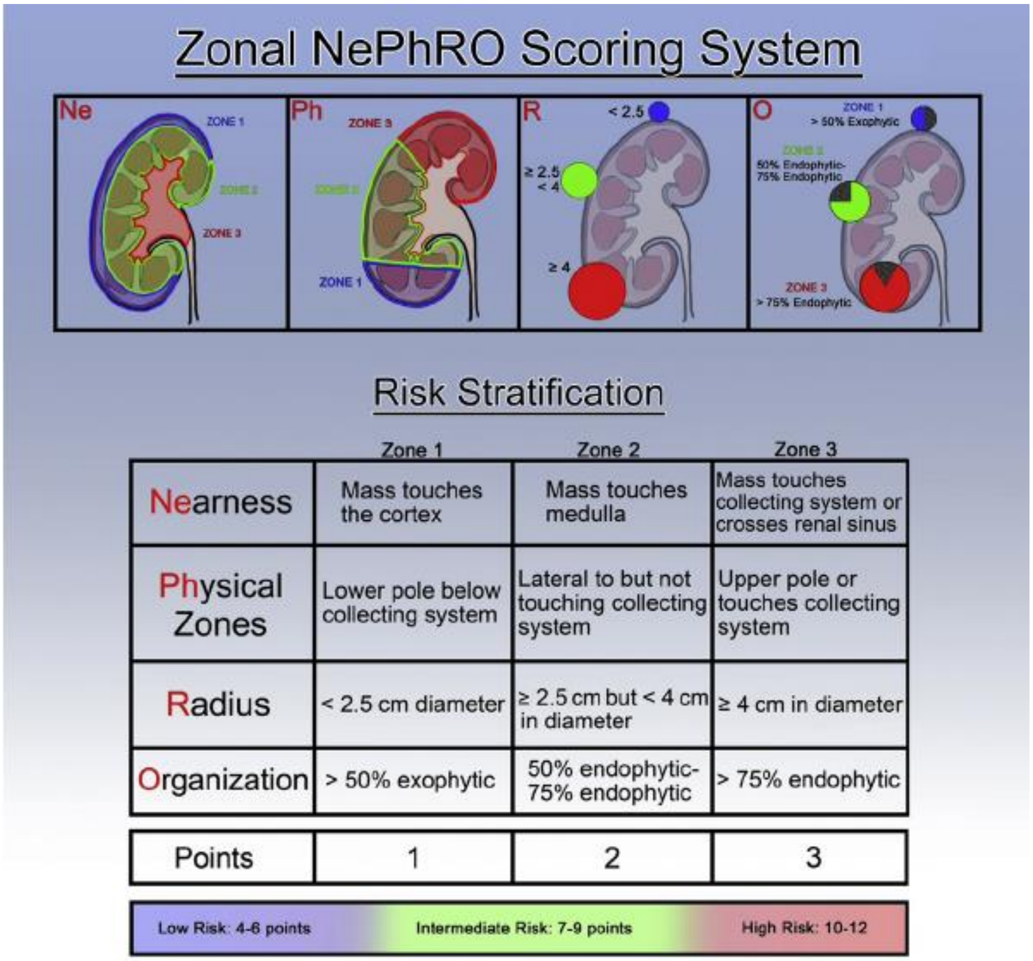


Utility
-Correlates with approach (radical vs partial/ open vs lap nephrectomy), duration, ischaemia time, blood loss, complications, renal function post-op, histology and grade
-Objective reporting and comparison of outcomes between groups

Criticism
-High measurement variability noted in some studies (E.g. collecting system anatomy variability in calculation of 'N', poor inter-observer concordance in drawing lines for 'L')
-Does not predict post operative renal function drop in patients with solitary kidney
-SRMs <4 cm may be suited to smaller radius scoring parameters as opposed to <4,4-7 and >7 cm
-Poor correlation with positive margins.
-Does not reflect complexity with reference to hilar nodal mass, tumour thrombus and local invasion

Other scoring systems

NePhRO scoring system (*Hakky et al. Clin Genitourin Can 2014*)



Zonal NePhRO Scoring System

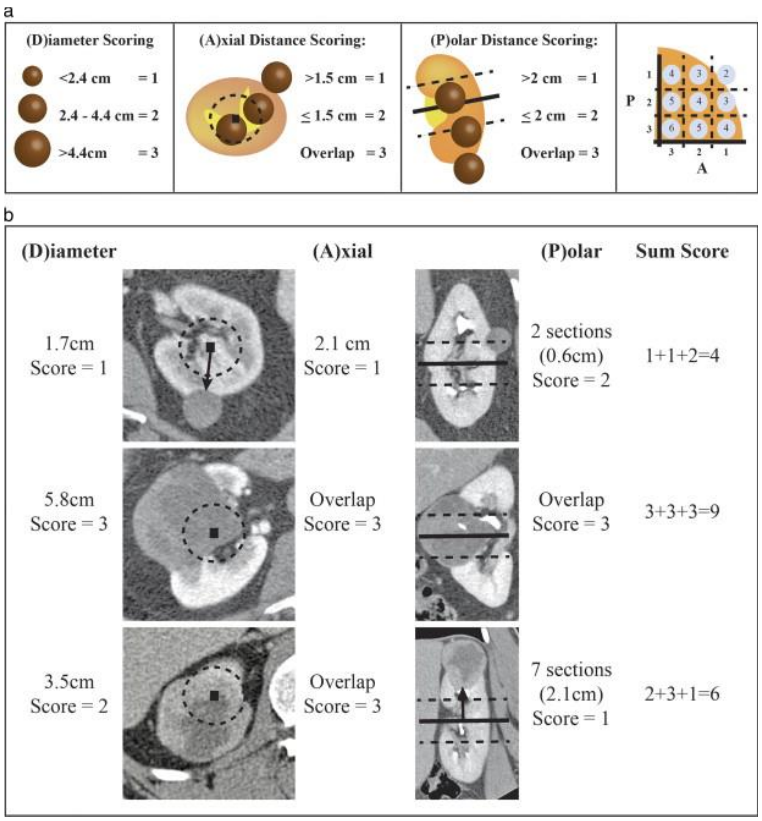
Risk Stratification

	Zone 1	Zone 2	Zone 3
Nearness	Mass touches the cortex	Mass touches medulla	Mass touches collecting system or crosses renal sinus
Physical Zones	Lower pole below collecting system	Lateral to but not touching collecting system	Upper pole or touches collecting system
Radius	< 2.5 cm diameter	≥ 2.5 cm but < 4 cm in diameter	≥ 4 cm in diameter
Organization	> 50% exophytic	50% endophytic-75% endophytic	> 75% endophytic
Points	1	2	3

Low Risk: 4-6 points | Intermediate Risk: 7-9 points | High Risk: 10-12

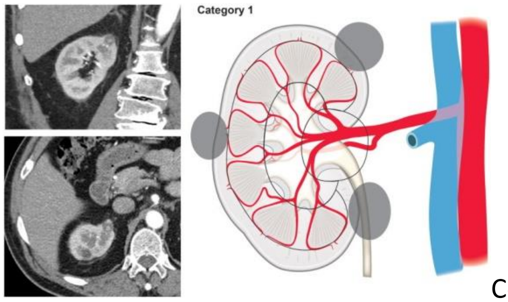
Simpler, easier to use, more predictive of post-op complications, better correlation with stage and complexity of SRM

DAP scoring system (*Simmons M et al. J Urol 2012*)

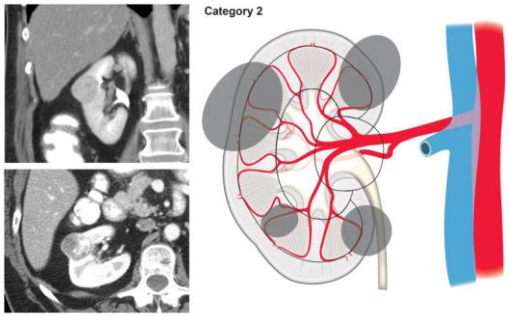


Predicts kidney volume preservation better, is simpler, less variable

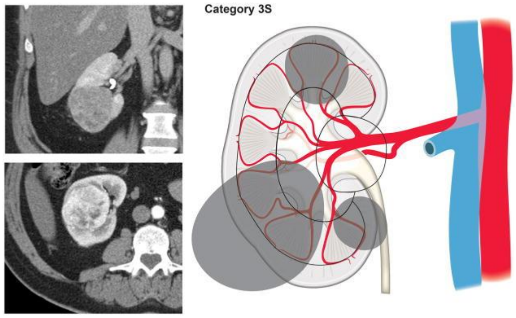
ABC (Arterial Based Complexity) system (*Spaliviero M et al. European Urology, 2016)*



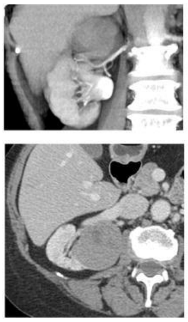
Cortical tumour involving interlobular + arcuate: Category 1

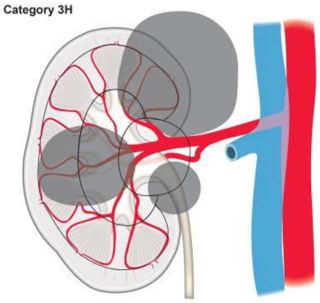


Iinterlobar arteries: Catergory 2



Segmental arteries + collecting system: Category 3S

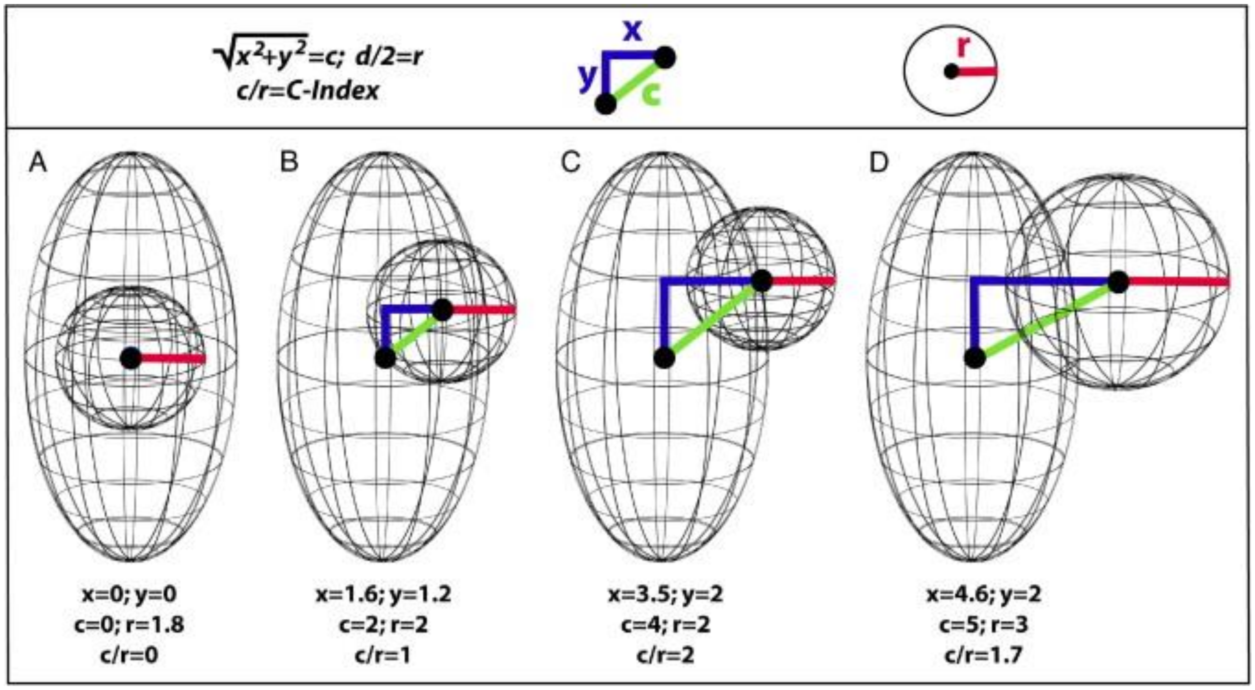




Hilum/ main vascular pedicle

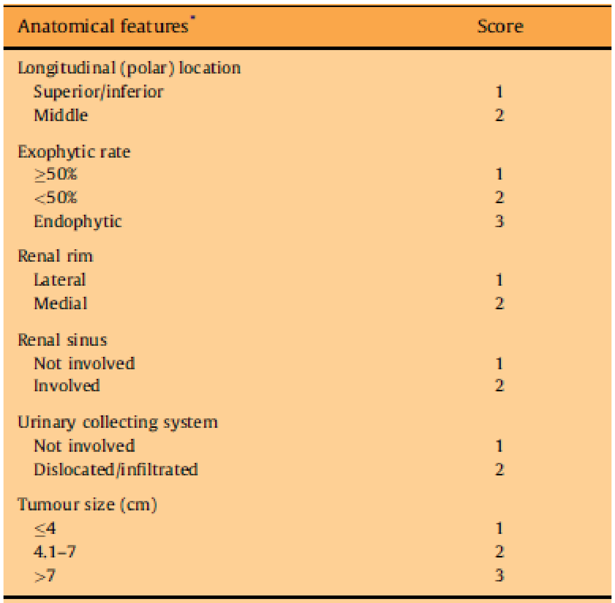
Correlated with ischaemia time, blood loss, urine leak and complexity of operation, easy to use

Centrality/ C index (***Simmons M et al. J Urol 2009)***

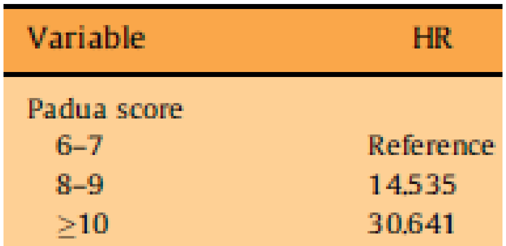


-Easy, reproducible, good prediction of operative difficulty
-Learning curve, calculation involved, kidney assumed to be uniform ellipse and tumour to be uniform sphere

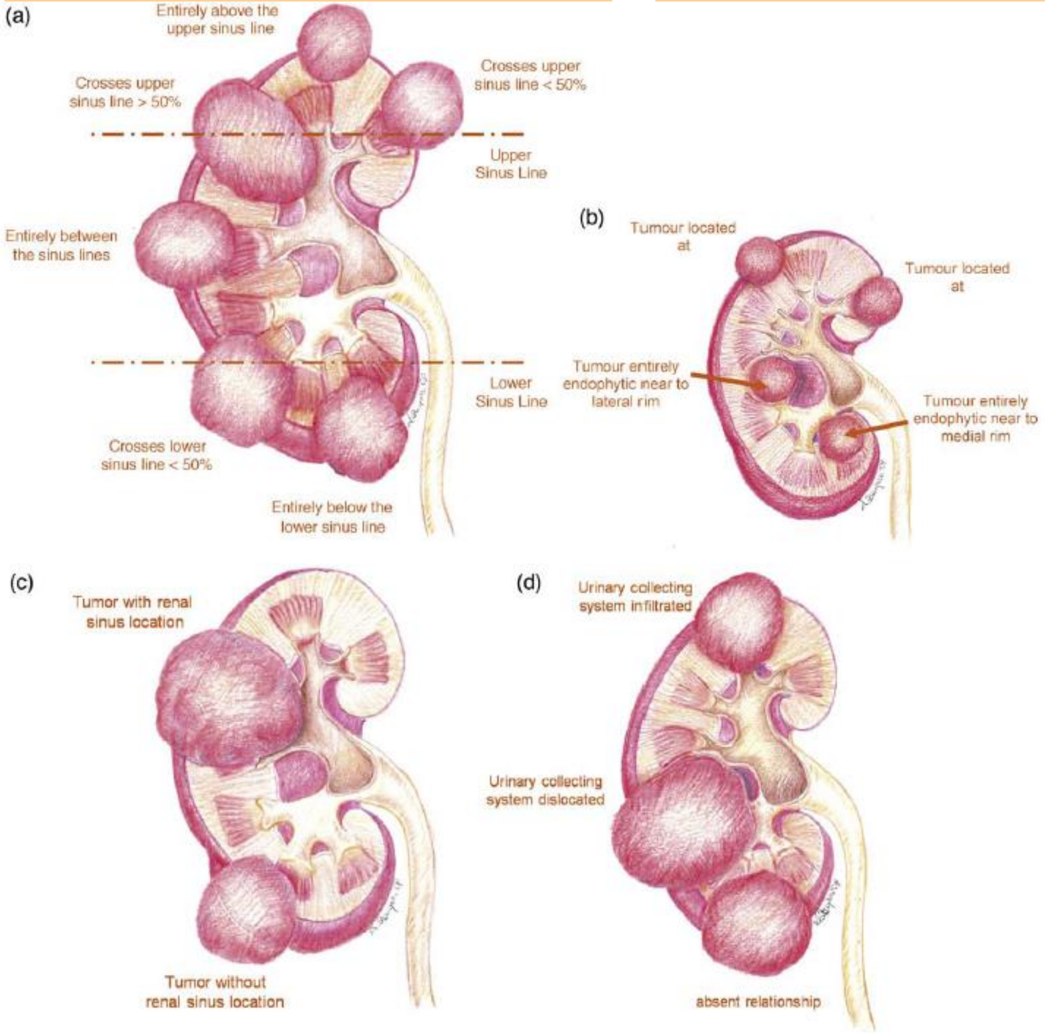
Pre-operative Aspects and Dimensions Used for an Anatomical classification-PADUA (Ficarra V et al. Eur Urol 2006)

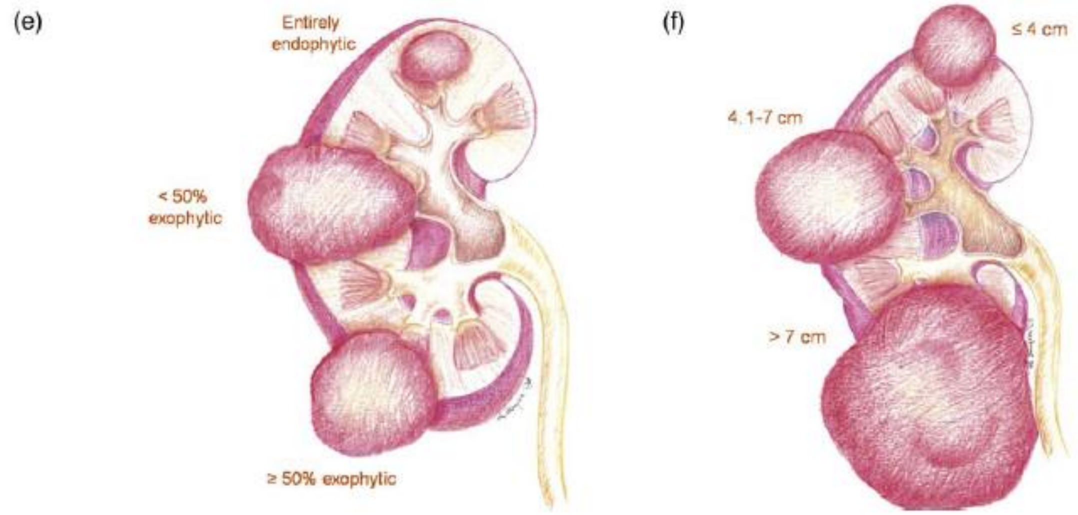


Anatomical features*	Score
Longitudinal (polar) location	
Superior/inferior	1
Middle	2
Exophytic rate	
≥50%	1
<50%	2
Endophytic	3
Renal rim	
Lateral	1
Medial	2
Renal sinus	
Not involved	1
Involved	2
Urinary collecting system	
Not involved	1
Dislocated/infiltrated	2
Tumour size (cm)	
≤4	1
4.1–7	2
>7	3



Variable	HR
Padua score	
6–7	Reference
8–9	14.535
≥10	30.641


(a)
Entirely above the upper sinus line
Crosses upper sinus line > 50%
Crosses upper sinus line < 50%
Upper Sinus Line
Entirely between the sinus lines
Lower Sinus Line
Crosses lower sinus line < 50%
Entirely below the lower sinus line
(b)
Tumour located at
Tumour located at
Tumour entirely endophytic near to lateral rim
Tumour entirely endophytic near to medial rim
(c)
Tumor with renal sinus location
Tumor without renal sinus location
(d)
Urinary collecting system infiltrated
Urinary collecting system dislocated
absent relationship


(e)
Entirely endophytic
< 50% exophytic
≥ 50% exophytic
(f)
≤ 4 cm
4.1-7 cm
> 7 cm

Bladder- BENIGN

1. **Pelvic lipomatosis (Engels' disease)**
    - PL is a rare, benign condition marked by exuberant pelvic overgrowth of non-malignant but infiltrative adipose tissue, usually in the abdominal and pelvic cavities.
    - Fat deposition generally occurs in the perivesical and perirectal spaces.
    - First described in 1959 by Engels
    - Mean age at presentation 48 years. About 2/3rd patients are blacks and 1/3rd white. Male-to-female ratio= 18:1
    - Etiology and incidence unknown
        - Obesity has been proposed to play a role, because radiographic improvement and worsening have been noted in response to weight loss and gain, respectively. Obesity has been noted in more than 50% of patients.
        - Genetic etiology may be possible
        - An abnormality in the chromatin-regulating high-mobility group-A (HMGA) proteins (gene on chromosome 12) has been implicated as a possible causative factor
        - Pelvic lipomatosis may be a chronic inflammatory response to UTIs.
    - **Presentation and physical findings**
        - Non-specific symptoms
        - Approximately 1/3rd patients present with LUTS, 1/4th with bowel symptoms, typically constipation. HTN reported in 1/3rd.
        - Suprapubic, back, flank, or perineal discomfort can be an initial manifestation.
        - Non-specific nature of these symptoms may result in delay in diagnosis
        - Physical findings may include a suprapubic mass, a high-riding prostate, and an indistinct pelvic mass.
    - **Diagnosis and evaluation**
        - On plain X-ray, increased pelvic lucency may be noted
        - IVU shows characteristic shape of bladder like a pear or gourd shape, extrinsically compressed and elongated, and the bladder base is frequently elevated
        - Proliferation of the mature fat in the pelvis and retroperitoneum may leads to bilateral hydronephrosis. PL causes medial displacement of the distal ureters (In contrast to RPF which usually causes medial deviation of proximal and midureters)
        - CT demonstrates pelvic fat, extrinsic compression of rectum. CT helps in differentiating PL from other pelvic masses e.g. lipomas, lipoplastic lymphadenopathy, and liposarcoma.
        - MRI permits characterization of fat and thus can make the diagnosis.
        - Evaluation should include cystoscopy
            - Some form of proliferative cystitis has been found in 75% of patients, including cystitis glandularis in up to 40%. Continued cystoscopic surveillance is also recommended in those with cystitis glandularis, because of the development of bladder adenocarcinoma.
            - Elongation of prostatic urethra, elevation of bladder neck, and pelvic fixation may cause difficult cystoscopic access. Cystoscopy may be impossible in 18%.
    - **Treatment**
        - Steroids, chemotherapy, radiotherapy, and chronic antibiotic therapy are not successful.
        - Surgical options in patients with obstructive uropathy secondary to PL include ureteral stenting, PCN, ureteral reimplantation, and urinary diversion with or without cystoprostatectomy.
        - Surgical intervention for removal of the pelvic lipomatous tissue is often limited, due to extensive deposits of fat, and their removal does not always lead to an improvement.
        - Pelvic exploration should be approached cautiously, because there is obliteration of normal anatomic planes and increased vascularity within the fatty mass.

2. **Malakoplakia**
    - Malacoplakia- Greek word meaning "soft plaque," is an unusual inflammatory disease that was originally described to affect the bladder but has been found to affect the genitourinary and gastrointestinal tracts, skin, lungs, bones, and mesenteric lymph nodes.
    - Described originally by Michaelis and Gutmann (1902), and characterized by von Hansemann (1903)→ as soft, yellow-brown plaques with granulomatous lesions in which the histiocytes contain distinct basophilic lysosomal inclusion bodies or Michaelis-Gutmann bodies.
    - **Pathogenesis**
        - Probably results from abnormal macrophage function in response to a bacterial infection, most often due to *E. coli.*
        - Association with compromised immune health status is well recognized

    - A defect in intraphagosomal bacterial digestion accounts for the unusual immunologic response that causes malacoplakia. Bacteria or bacterial fragments form nidus for the calcium phosphate crystals that laminate the Michaelis-Gutmann bodies.
- **Pathology**
    - Diagnosis is made by biopsy.
    - Lesion is characterized by large histiocytes, known as *von Hansemann cells*, and small basophilic, extracytoplasmic, or intracytoplasmic calculospherules called Michaelis-Gutmann bodies, which are pathognomonic (but not necessary for diagnosis)
    - Macrophages from other pathologic processes closely resembling malacoplakia but without MG bodies do not contain α1- antitrypsin.□Thus immunohistochemical staining for α1-antitrypsin may be a useful test for an early and accurate differential diagnosis of malacoplakia.
- **Clinical Presentation**
    - **Most patients are older than 50 years**
    - Females to males ratio for malacoplakia of urinary tract is 4:1
    - Patients often are debilitated, are immunosuppressed, and have other chronic diseases.
    - Bladder malacoplakia causes bladder irritability and hematuria because of mucosal plaques or nodules. These lesions progress and form fungating, firm, sessile masses that cause filling defects of the bladder, ureter, or pelvis on IVU.
    - Strictures of distal ureter may become strictured or stenotic and cause subsequent renal obstruction or nonfunction (Sexton et al, 1982). A typical patient with renal parenchymal disease may have one or more radiographic masses and chronic

3. Pathogenesis and management of calculi in augmentation cystoplasty

- **Etiopathogenesis:** Patients with augmented bladders are at increased risk of stone formation. Incidence may be 10-20%. Causative factors include:
    - Urinary stasis and recurrent infection are the most common causes. Persistent infection leads to the development of calcium magnesium ammonium phosphate stones. **UTI with urea-splitting organism causes persistent alkalinization** of the urine which predisposes to phosphate stone formation.
    - Another major cause of stone formation in augmented bladders is a foreign body such as nonabsorbable suture, and prolonged indwelling catheters
    - Hyperchloremic metabolic acidosis (these patients are also susceptible for renal calculi)
    - Persistent hypercalciuria and alterations of urinary excretion products associated with use of bowel in urinary system.
    - Alterations in intestinal mucus, particularly in the presence of infection or obstruction, may serve as a nidus or interfere with emptying and thereby exacerbate infection and stone formation
    - Patients with neurogenic bladder in whom augmentation is performed have additional risk factors such as pelvicaliectasis, VUR, renal scarring, bowel dysfunction and thoracic spinal defect.
- **Diagnosis**
    - Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.
- **Management**
    - The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols
    - Efficient long-term stone prevention as well as treatment in such patients requires correction of the metabolic acidosis and any related metabolic problem, appropriate infection control, and restoration of normal storage and voiding function of the augmented bladder.
    - Patients with myelomeningocele commonly have latex allergy, therefore, appropriate measures need to be taken. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia.
    - Endoscopic and percutaneous management of augmented-bladder stones is preferred as open surgery is difficult. However,
        - Endoscopic management may be relatively difficult (than in patients with normal bladders) because of distorted anatomy and risk of perforation.
        - PCCL may also be difficult because of prior surgery and bowel loops in the planned path of access. Ultrasound guided percutaneous puncture is extremely useful.
    - Open surgery
        - Reserved for failed or impossible endoscopic and percutaneous removal of stones
        - Difficult because of adhesion of prior surgery
        - Risk of injury to the vascular pedicle of bowel segment used for augmentation

4. Mitrofanoff principle

- Mitrofanoff (1980) described a continence mechanism with use of the appendix and ureter to make a flap valve.
- **Principle**
  - It is based on the principle that any tubular structure could be implanted effectively into a low-pressure reservoir. The foundation for the success of the Mitrofanoff principle is based on construction of a submucosal tunnel for a supple, small diameter conduit. As the reservoir fills, rise in Intravesical pressure is transmitted through the epithelium and to the implanted conduit, coapting/compressing its lumen, thereby providing an effective continence mechanism.
- **Advantage of use of Mitrofanoff principle**
  - Major advantage of Mitrofanoff is that it avoids multiple potential complications associated with harvesting of the ileocecal valve (for continence) or use of other bowel segments. This is particularly important in children.
- **Advantages of use of appendix**
  - Appendix is an ideal natural tubular structure that can be safely removed.
  - Small caliber of the appendix facilitates construction of a short functional tunnel with the bladder wall.
  - Continence can be achieved with only as small as 2cm of appendiceal tunnel.
  - Has provided good results as continence mechanism in both continent urinary reservoirs and native bladders.
  - Particularly useful in children because it is relatively longer and the abdominal wall generally thinner.
  - Mesoappendix allows easy mobilization of the appendix for use in native bladder or virtually any reservoir.
  - Can be used as in-situ along with right colon in a continent urinary reservoir with good results.
- **Technique**
  - Appropriate skin incision to allow adequate mobilization of the appendix to the bladder. This can be achieved through a low midline or a transverse incision.
  - Once the cecum is mobilized, base of the appendix is amputated with a small cuff of cecal wall, and cecum is closed. Use of the cuff for external stoma reduces the risk of stomal stenosis.
  - If the length of the appendix is lesser, a greater portion of the cecum can be harvested and tubularized with the appendix.
  - Distal end of appendix is amputated. Typically, the distal end of the appendix is tunneled into a posterolateral position within the bladder, and base of the appendix (cecal end) is brought to the abdominal wall.
  - Silastic stent is typically left for 10 to 14 days within the efferent catheterizable channel.
  - Catheterization should be repeated at least every 4 hours during the day for reservoir drainage, maintenance of patency, and to minimize of the risk of stomal stenosis.

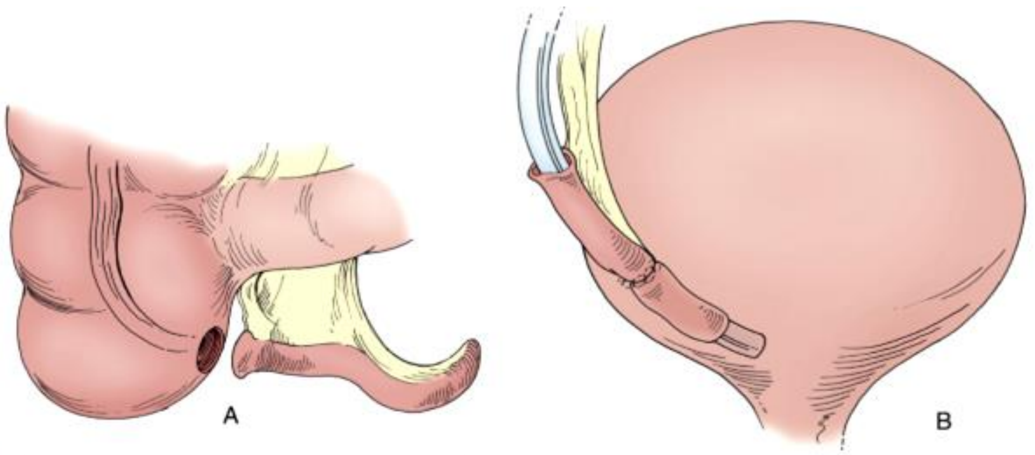
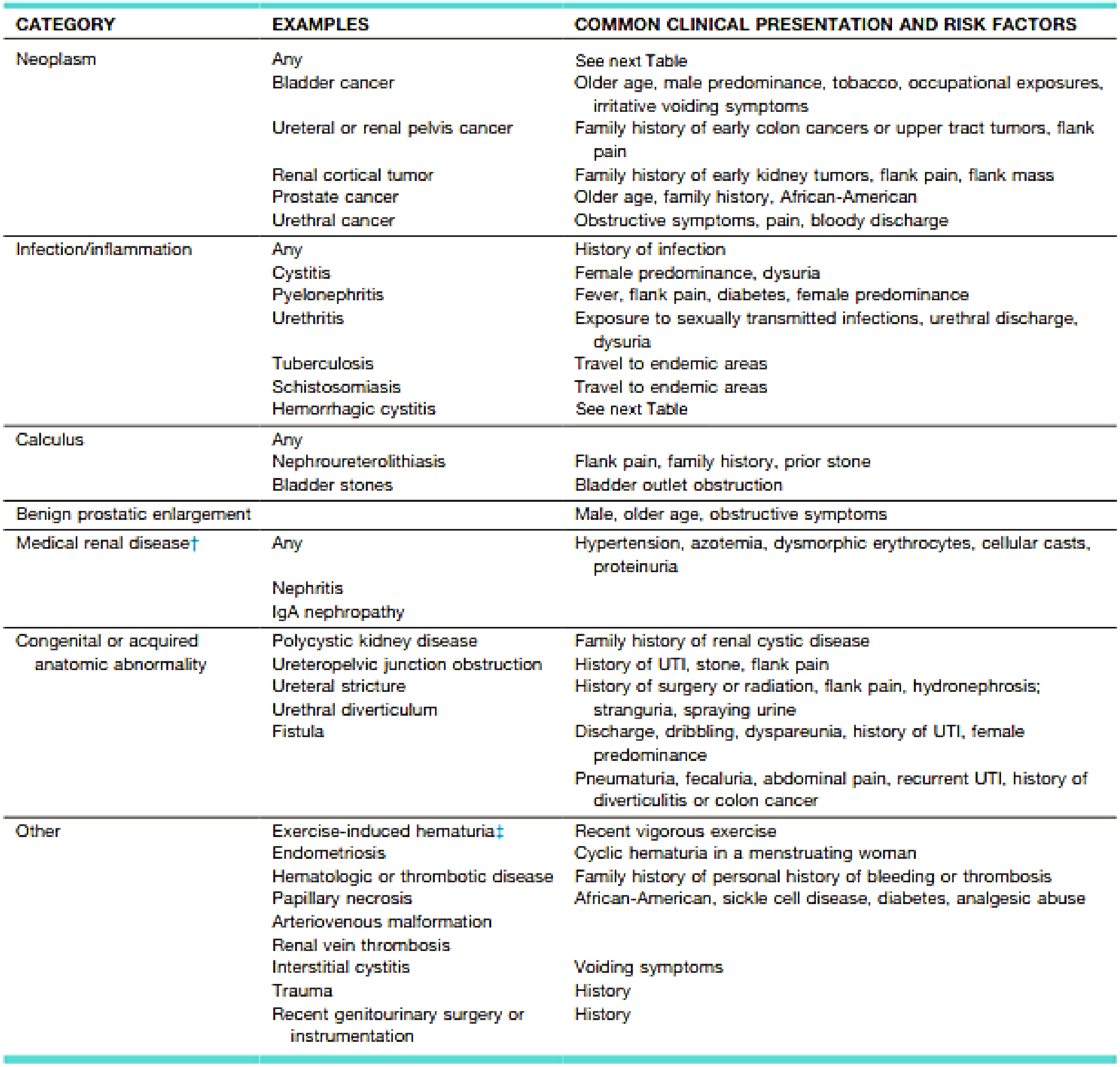


Figure 129–19. Appendicovesicostomy. **A**, The appendix is harvested with a cuff of cecum on a wide pedicle based on the appendiceal artery. A flap of cecum can be harvested in continuity with the appendix and tubularized to increase the length. **B**, The distal appendix is tunneled into the bladder to provide continence after the end is amputated. The proximal end of the appendix, the cecal cuff, is brought to the umbilicus or right lower quadrant as a catheterizable stoma.

- **Problems and Complications**
  - Appendix may not be available in all patients because of previous appendectomy, its location or length, congenital absence, involvement with adhesions etc.
  - Complications of bowel handling and appendicectomy or bowel resection.

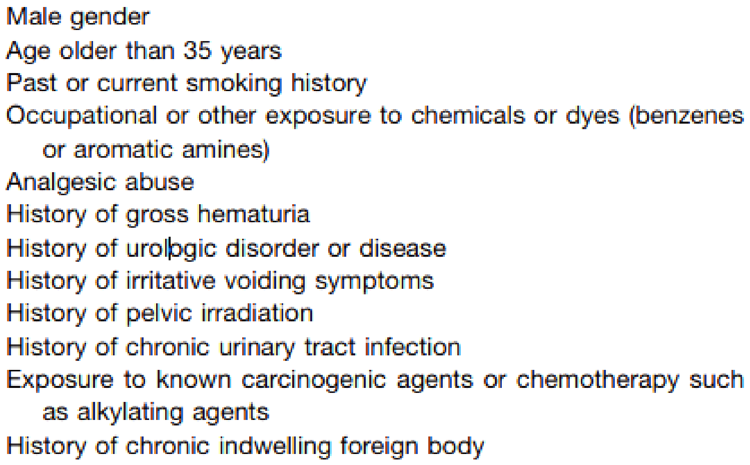
    - Incontinence: is rare event with Mitrofanoff principle. It may result from inadequate length of tunnel or persistently elevated reservoir pressure.
    - Stomal stenosis: is the most common complication occurring in 6% to 10% of patients.
    - Kinking of catheterizable channel

5. **Evaluation and management of microscopic haematuria (MH)**
    - **Definition and diagnostic criteria of MH:** MH is a sign rather than a symptom, and is defined as the presence 3 or more RBCs on microscopic examination of urine. **Prevalence of MH among healthy participants is 6.5%,** with higher rates in males, older patients, and smokers. It is important to realize that a small number of RBCs may be present in urine under normal circumstances e.g., sexual activity, exercise etc.
    - AUA guidelines advise that **a single positive urinalysis for MH should be evaluated further,** based on a meta-analysis that found that the rate of malignancy detected among patients evaluated for a single positive urinalysis was **3.6% (1.8% to 4.3%).**
    - **Requirement for diagnosis of MH**
        - **Positive urine dipstick (chemical test) for blood must be confirmed on urinalysis with microscopy. Furtehr evaluation should not be based on positive dipstick test ONLY.**
        - If urinalysis (microscopy) is not confirmatory, but there is suspicion repeat microscopic testing justified.
        - Specimens collected immediately after prolonged recumbency (first void in morning) or after vigorous physical or sexual activity may result in false positivity for MH. Dilute urine may result in false-negative.
    - **Evaluation of MH**
        - One third to two thirds (2/3rd – 1/3rd) of patients evaluated for MH have a demonstrable cause (Table 1)
        - Risk of finding a malignancy is higher among patients with higher levels of MH (>25 RBCs/hpf), gross hematuria, or risk factors for malignancy
        - **Differential Diagnosis of Asymptomatic MH→ Table 1**
            - It is important to rule out obvious benign causes, such as menstruation, recent instrumentation, uncomplicated cystitis before proceeding to D/D.
            - Hematologic illness, medical renal disease, or use of anticoagulants or antiplatelets does NOT preclude the need for further evaluation.



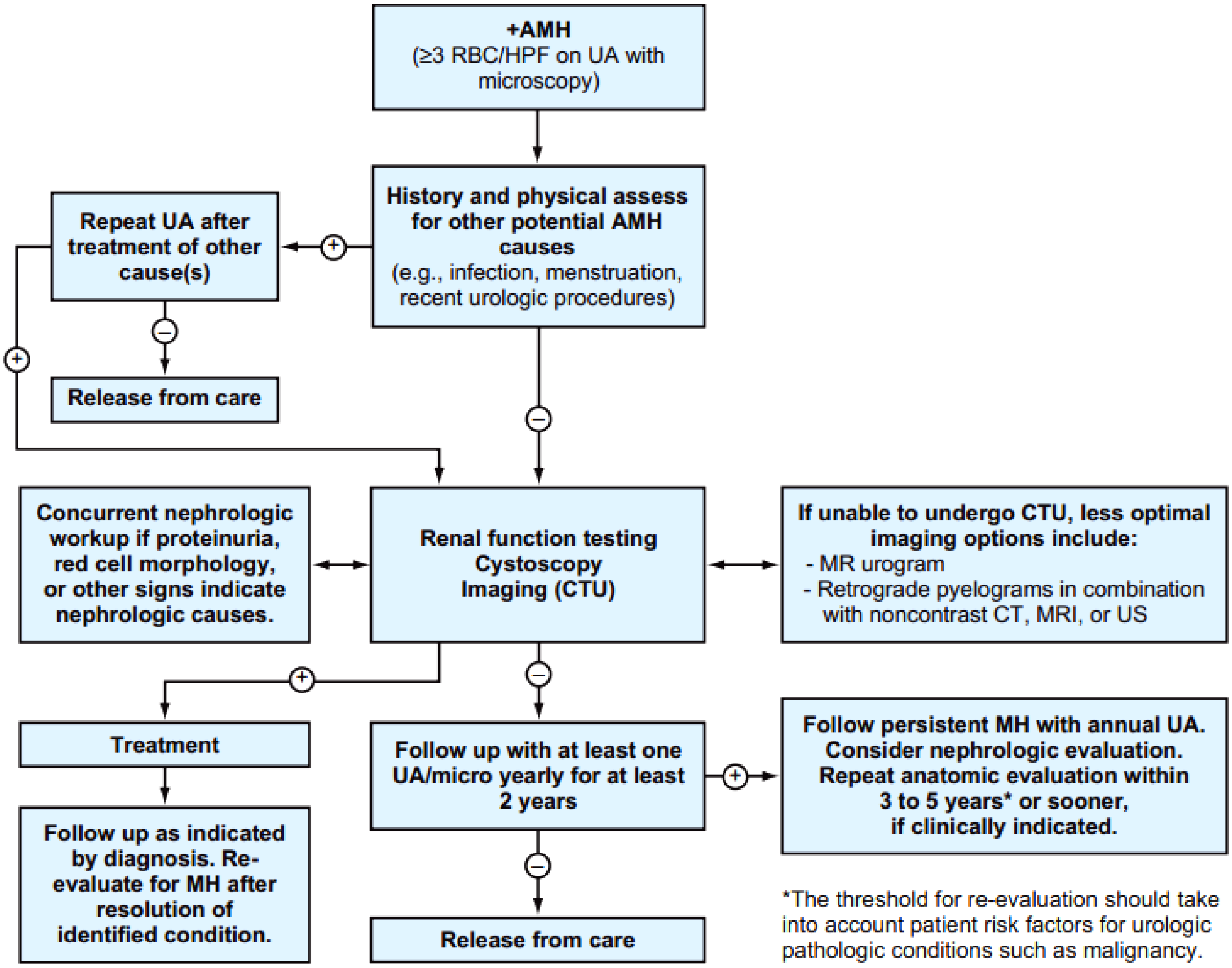
CATEGORY	EXAMPLES	COMMON CLINICAL PRESENTATION AND RISK FACTORS
Neoplasm	Any	See next Table
	Bladder cancer	Older age, male predominance, tobacco, occupational exposures, irritative voiding symptoms
	Ureteral or renal pelvis cancer	Family history of early colon cancers or upper tract tumors, flank pain
	Renal cortical tumor	Family history of early kidney tumors, flank pain, flank mass
	Prostate cancer	Older age, family history, African-American
	Urethral cancer	Obstructive symptoms, pain, bloody discharge
Infection/inflammation	Any	History of infection
	Cystitis	Female predominance, dysuria
	Pyelonephritis	Fever, flank pain, diabetes, female predominance
	Urethritis	Exposure to sexually transmitted infections, urethral discharge, dysuria
	Tuberculosis	Travel to endemic areas
	Schistosomiasis	Travel to endemic areas
	Hemorrhagic cystitis	See next Table
Calculus	Any	
	Nephroureterolithiasis	Flank pain, family history, prior stone
	Bladder stones	Bladder outlet obstruction
Benign prostatic enlargement		Male, older age, obstructive symptoms
Medical renal disease†	Any	Hypertension, azotemia, dysmorphic erythrocytes, cellular casts, proteinuria
	Nephritis	
	IgA nephropathy	
Congenital or acquired anatomic abnormality	Polycystic kidney disease	Family history of renal cystic disease
	Ureteropelvic junction obstruction	History of UTI, stone, flank pain
	Ureteral stricture	History of surgery or radiation, flank pain, hydronephrosis; stranguria, spraying urine
	Urethral diverticulum	Discharge, dribbling, dyspareunia, history of UTI, female predominance
	Fistula	Pneumaturia, fecaluria, abdominal pain, recurrent UTI, history of diverticulitis or colon cancer
Other	Exercise-induced hematuria‡	Recent vigorous exercise
	Endometriosis	Cyclic hematuria in a menstruating woman
	Hematologic or thrombotic disease	Family history of personal history of bleeding or thrombosis
	Papillary necrosis	African-American, sickle cell disease, diabetes, analgesic abuse
	Arteriovenous malformation	
	Renal vein thrombosis	
	Interstitial cystitis	Voiding symptoms
	Trauma	History
	Recent genitourinary surgery or instrumentation	History

- **Risk factors for urinary tract malignancy in patients with MH→ Table 2**



Male gender
Age older than 35 years
Past or current smoking history
Occupational or other exposure to chemicals or dyes (benzenes or aromatic amines)
Analgesic abuse
History of gross hematuria
History of urologic disorder or disease
History of irritative voiding symptoms
History of pelvic irradiation
History of chronic urinary tract infection
Exposure to known carcinogenic agents or chemotherapy such as alkylating agents
History of chronic indwelling foreign body

- **Evaluation: Algorithm from AUA guidelines. [AMH- Asymptomatic MH, UA- Urinalysis]**


+AMH
(≥3 RBC/HPF on UA with microscopy)
History and physical assess for other potential AMH causes
(e.g., infection, menstruation, recent urologic procedures)
+
Repeat UA after treatment of other cause(s)
−
Release from care
+
−
Concurrent nephrologic workup if proteinuria, red cell morphology, or other signs indicate nephrologic causes.
Renal function testing
Cystoscopy
Imaging (CTU)
If unable to undergo CTU, less optimal imaging options include:
- MR urogram
- Retrograde pyelograms in combination with noncontrast CT, MRI, or US
+
Treatment
Follow up as indicated by diagnosis. Re-evaluate for MH after resolution of identified condition.
−
Follow up with at least one UA/micro yearly for at least 2 years
+
Follow persistent MH with annual UA. Consider nephrologic evaluation. Repeat anatomic evaluation within 3 to 5 years* or sooner, if clinically indicated.
−
Release from care

*The threshold for re-evaluation should take into account patient risk factors for urologic pathologic conditions such as malignancy.

- **Cystoscopy in the evaluation of MH**
    - Cystoscopy is the most reliable way to evaluate the bladder for the presence of bladder cancer and also evaluates the urethra. Cystoscopy should be performed in all adults with criteria for MH evaluation who are 35 years of age or older and/or have risk factors for malignancy (Table 2). Cystoscopy may be omitted in persons younger than age 35 years without risk factors.
- **Upper Tract Imaging**
    - **Multiphasic CT urogram is the imaging study of choice for the evaluation of asymptomatic MH, as it** offers complete imaging of the urinary tract and has the highest sensitivity and specificity for detecting renal parenchymal and urothelial lesions.
    - In cases where CT urography cannot be used (e.g., pregnancy, contrast allergy, renal insuffciency), MRI may be used.
    - If MRI is contraindicated (e.g. pacemaker, significant renal function compromise with eGFR <30) , NCCT or USG combined with RGP may be most appropriate.
- **Follow up of patients with negative evaluation**
    - Annual urinalysis for 2 years after a complete negative hematuria workup
    - Patient can be released from care if the urinalyses confirm resolution of MH
    - Repeat hematuria evaluation within 3 to 5 years in cases of persistent or recurrent asymptomatic MH or development of symptoms or GH

6. Pathogenesis and management of bladder diverticulae (BD)

- BD represents herniation of bladder mucosa (urothelium) through the muscularis propria of the bladder wall. This results in a thin-walled, urine-filled structure adjacent to and connecting with bladder lumen through a variably sized neck, or ostium. Histologically, BD w**all is composed of mucosa, subepithelial connective tissue or lamina propria, some scattered thin muscle fibers, and an adventitial layer. Because of lack of organized and functional muscles in the wall,** emptying of BD is usually poor leading to large PVRs.

- **Classification and etiopathogenesis**
  - **Congenital BD**
    - Usually present during childhood, with a peak incidence at 10 years of age, and occur most commonly in males.
    - Usually solitary, located lateral and posterior to ureteral orifice, and often associated with VUR. They are usually larger in size than acquired BD.
    - Primary cause appears to be congenital weakness at the level of UVJ and not BOO
    - Most common presentation is UTI.
    - Congenital BD may occur in the presence of normal voiding dynamics (and in the absence of BOO) but secondary BOO may develop because of BD itself.
    - Typically, congenital BD are found in smooth-walled bladders without trabeculations.
    - Congenital BD have association with a number of congenital syndromes [Menkes syndrome (kinky hair or copper defciency syndrome), Williams syndrome, Ehlers-Danlos syndrome, and fetal alcohol syndrome]
  - **Acquired BD (Secondary BD)**
    - Most commonly occur in the setting of BOO or neurogenic vesicourethral dysfunction.
    - Similar to the congenital BD, these BD are also located most commonly at VUJ, but also occur elsewhere in bladder.
    - Acquired diverticulae in males usually occur after 60 years of age, which corresponds to the age of the development of prostatic enlargement.
    - Approximately 70% of acquired diverticulae are associated with BPE.
    - Acquired diverticulae are often multiple, typically found in association with significant bladder trabeculation, and much more common in males.
    - Acquired diverticulae in females are relatively uncommon and often associated with BOO secondary to dysfunctional voiding, vaginal prolapse, bladder neck hypertrophy, urethral stricture, or iatrogenic obstruction resulting from anti-incontinence surgery.
    - Common causes in children and young adults include bladder neck dysfunction, PUV, and neurogenic vesicourethral dysfunction.
    - Iatrogenic acquired BD can occur due to inadequate closure of muscular layers of bladder wall following cystotomy, or following ureteral reimplantation surgery at the site of ureteroneocystostomy.
    - BD located supero-lateral to the ureteral orifice without involving the trigone in the setting of a neuropathic bladder and VUR is called “Hutch” diverticulum.
- **Presentation**
  - Size of BD does not to correlate with symptoms or complications.
  - Acquired BD do not typically produce specific symptoms and are most often found incidentally in the evaluation of other signs and symptoms, especially UTI or symptoms of LUTS/BOO. Large BD may produce symptoms related to urinary stasis or its mass effect in lower abdomen and pelvis, including incomplete bladder emptying, lower abdominal fullness, and double voiding.
  - Congenital BD most often present with UTI.
- **Evaluation**
  - Initial evaluation of BD includes thorough history and physical examination, including DRE. In the male, PSA should be done where appropriate.
  - History should quantitate LUTS, query potential occult sources of neurogenic vesicourethral dysfunction (spinal surgery, etc.), and any prior lower urinary tract surgery.
  - Urinalysis, urine culture, and urine cytology should be considered in most patients. Pyuria and hematuria are often present. In fact, persistent pyuria unresponsive to antibiotic therapy may be an indication for bladder diverticulectomy in an otherwise asymptomatic patient.
  - Further evaluation for BOO, and endoscopic examination and imaging of the lower and upper urinary tract should be performed.
  - **Imaging:** Diagnosis of BD relies on radiographic and endoscopic findings.
    - **Fluoroscopically monitored VCUG** is an excellent study to detect BD. Anterior-posterior, oblique, lateral images with post-void film provides information about anatomy, location, and size along with associated VUR, emptying of the bladder diverticulum with voiding.
    - **Cross-sectional imaging of lower urinary tract** provides useful information regarding BD and surrounding structures and relations. Any lesion inside BD can also be detected and further evaluation can be pursued. Cross-sectional imaging provides surgically relevant information including the location of ureters and surrounding structures (rectum, etc.).
    - **Imaging of the upper tracts** includes IVU, USG, CT, or MRI. Goal of upper tract imaging in adults is to evaluate for asymptomatic/silent HUN which can occur in up to 7%. In children with BD is commonly associated with upper tract abnormalities such as renal scarring, dysplasia

        and HDN in up to 30%. BD may cause deviation with or without compression of the ipsilateral ureter. Medial deviation of the pelvic ureter is most commonly seen; however, lateral deviation may also occur.
    - **PFS** are indicated in patients with NVD and BD. But their role is not well defined.
    - **Endoscopic (cystoscopic) examination** should be performed to inspect the bladder and the entire inside of BD for stones or tumor. Location of BD relative to ureteric orifices and bladder neck, number and size should be noted**.** Any abnormal-appearing epithelium or lesions within the diverticulum are biopsied with extreme care to prevent perforation.

- **Management**
  - **General rule** states that, if BOO is the cause of BD, definitive treatment of BOO should be undertaken before formal treatment of BD. BD should be reassessed following relief of BOO, and if bladder emptying is satisfactory and symptoms resolve, the BD may not require surgical excision. However, open bladder diverticulectomy + open prostatectomy or TURP can be performed simultaneously.
  - **Management options** include observation, endoscopic management, and surgical excision.
  - **Observation/Nonsurgical Management**
    - Adult patients with minimal symptoms and no complicating factors may opt for observation with surveillance.
    - Should be counselled about higher risk of malignancy and need for periodic reassessment.
    - Symptoms and signs that indicate progression include increasing LUTS, hematuria, and UTI.
    - Patients who are unfit for surgery, unwilling for surgery, remain symptomatic or have poor bladder emptying even after relief of BOO may be effectively treated with CIC.
    - In children, observation and medical management are usually offered to those with associated syndromes, or connective tissue disorders.
  - **Indications for Intervention**
    - To treat LUTS related to BD that are not otherwise responsive to medical management
    - Complications directly related BD→ persistent symptoms, chronic recurrent UTI, stones within the diverticulum, malignancy or premalignant change, and upper tract deterioration due to obstruction or VUR.
    - Poor surgical-risk patients because of advanced age or medical illness should not undergo surgical excision but may be candidates for CIC or endoscopic treatment.
  - **Endoscopic Management**
    - May be considered in aged or debilitated patients, unfit for an open operation, or those undergoing TURP
    - Includes **TUR of diverticular neck which is** performed with standard resectoscope using loop or Collins knife. Circumferential resection of the entire neck may be performed, and can be **combined with fulguration of the entire urothelial lining of BD which** results in obliteration of the diverticulum or reduction in its size.
    - This technique is less successful in large BD.
  - **Open Surgical Management**
    - **Principles of diverticulectomy**
      - i. Full mobilization of the diverticular sac, including the neck
      - ii. Excision of the sac
      - iii. Closure of the bladder
    - Bladder is most commonly approached extraperitoneally through a low midline or transverse
      incision. Retropubic space is entered and developed.
    - Diverticulectomy can be performed via transvesical (most common approach), extravesical and combined approaches. Dissection should be careful to avoid ureteral injury, because BD is usually located adjacent to or adherent to the ureter. Ureteral stents are often placed preoperatively or intraoperatively to facilitate dissection and avoid ureteric injury.
    - TURP or open suprapubic prostatectomy (if indicated) can be performed concomitantly with transvesical bladder diverticulectomy.
  - **Laparoscopic and Robotic Diverticulectomy** has also been reported via transperitoneal and transvesical approaches.

CA bladder

Q1: Complications of intestinal segments in Urology (essay)

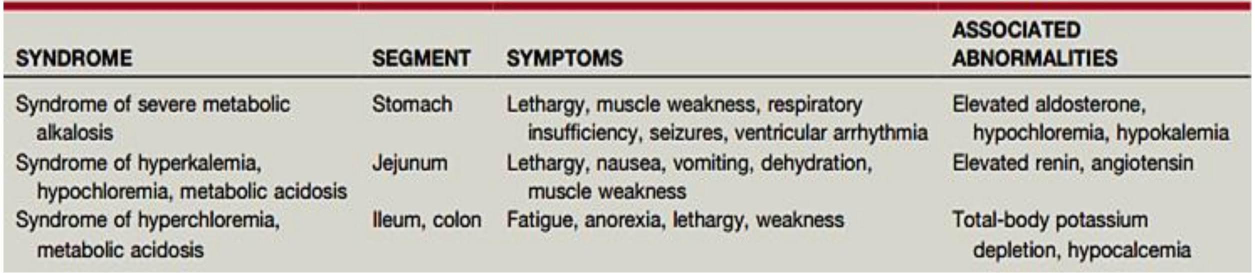
Ans: Mainly 3 classes

I. **Metabolic:** result from altered solute reabsorption by the intestine of the urine that it contains.
II. **Neuromechanical:** aspects involve the configuration of the gut, which affects storage volume and contraction of the intestine that may lead to difficulties in storage.
III. **Technical-surgical:** involve aspects of the procedure that result in surgical morbidity. These are specific to the type of intestinal segment used and procedure performed.

METABOLIC

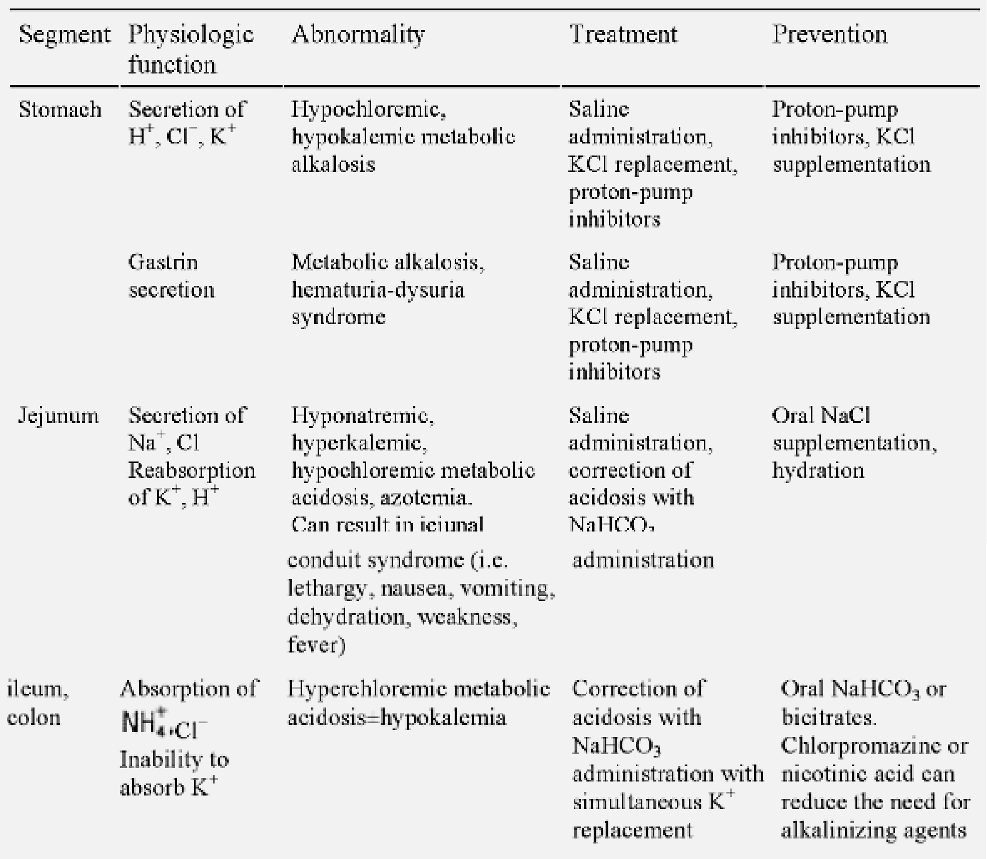
- **Factors influencing the amount and type of absorption from the bowel segment include:**
  - Segment of bowel used
  - Surface area of the bowel used
  - Amount of time the urine is exposed to the bowel (retentive or non-retentive diversion)
  - Concentration of solutes in the urine
  - Renal function
  - pH of the fluid in contact with bowel

1) **Electrolyte abnormalities:** The syndromes of electrolyte abnormalities in patients with use of bowel segments are as follows



SYNDROME	SEGMENT	SYMPTOMS	ASSOCIATED ABNORMALITIES
Syndrome of severe metabolic alkalosis	Stomach	Lethargy, muscle weakness, respiratory insufficiency, seizures, ventricular arrhythmia	Elevated aldosterone, hypochloremia, hypokalemia
Syndrome of hyperkalemia, hypochloremia, metabolic acidosis	Jejunum	Lethargy, nausea, vomiting, dehydration, muscle weakness	Elevated renin, angiotensin
Syndrome of hyperchloremia, metabolic acidosis	Ileum, colon	Fatigue, anorexia, lethargy, weakness	Total-body potassium depletion, hypocalcemia

Mechanism of hyperchloremic metabolic acidosis is transport of **ammonium**. Ammonium substitutes for sodium in the Na+-H+ antiport. The **exchange of the weak acid NH4 for a proton is coupled with the exchange of bicarbonate for chloride**. Thus **ammonium chloride** is absorbed across the lumen into the blood in exchange for carbonic acid (i.e., CO2 and water).



Segment	Physiologic function	Abnormality	Treatment	Prevention
Stomach	Secretion of H^+, Cl^-, K^+	Hypochloremic, hypokalemic metabolic alkalosis	Saline administration, KCl replacement, proton-pump inhibitors	Proton-pump inhibitors, KCl supplementation
	Gastrin secretion	Metabolic alkalosis, hematuria-dysuria syndrome	Saline administration, KCl replacement, proton-pump inhibitors	Proton-pump inhibitors, KCl supplementation
Jejunum	Secretion of Na^+, Cl Reabsorption of K^+, H^+	Hyponatremic, hyperkalemic, hypochloremic metabolic acidosis, azotemia. Can result in jejunal conduit syndrome (i.e. lethargy, nausea, vomiting, dehydration, weakness, fever)	Saline administration, correction of acidosis with $NaHCO_3$ administration	Oral NaCl supplementation, hydration
ileum, colon	Absorption of NH_4^+,Cl^- Inability to absorb K^+	Hyperchloremic metabolic acidosis=hypokalemia	Correction of acidosis with $NaHCO_3$ administration with simultaneous K^+ replacement	Oral $NaHCO_3$ or bicitrates. Chlorpromazine or nicotinic acid can reduce the need for alkalinizing agents

2) **Renal deterioration**
   a. Incidence of renal deterioration after conduit urinary intestinal diversion has varied from 10% to 74%
   b. Significant and progressive deterioration in renal function occurs in the majority of patients independent of the type of urinary diversion
   c. The most common cause of death in patients with ureterosigmoidostomy for more than 15 years is acquired renal disease (i.e., sepsis or renal failure)
   d. In patients with ileal conduits, about 6% ultimately die of renal failure

3) **Altered sensorium:** may occur due to
   a. Magnesium deficiency
   b. Drug intoxication
   c. Abnormalities in ammonia metabolism→ Most common cause

   More common in patients with altered LFT

4) **Abnormal drug metabolism**
   a. Drugs more likely to be problematic are those absorbed by GIT and excreted unchanged by kidney. Thus the excreted drug is re-exposed to the intestinal segment, which then reabsorbs it, and toxic serum levels develop. This has been reported with phenytoin, and with certain antibiotics.
   b. Methotrexate toxicity has been documented in a patient with an ileal conduit via similar mechanism. Thus, in patients with continent diversions who are receiving chemotherapy, consideration should be given to draining the pouch while the toxic drugs are being administered.

5) **Osteomalacia or renal rickets**
   a. Occurs when mineralized bone is reduced and the osteoid component becomes excessive
   b. Most commonly reported in patients with ureterosigmoidostomies
   c. Cause of osteomalacia may be multifactorial but commonly involves
      i. Persistent metabolic acidosis which is buffered by bone with release of bone calcium
      ii. Vitamin D resistance (likely renal origin)
      iii. Excessive calcium loss by kidney

6) **Growth retardation**
   a. Urinary intestinal diversion has a detrimental effect on growth and development
   b. Patients with long-term urinary diversions are more susceptible to fractures and to complications after orthopedic procedures.

7) **Persistent and recurrent infections**
   a. There is increased incidence of bacteriuria, bacteremia, and septic episodes
   b. In patients with intestinal cystoplasty 13% have septic and major infectious complications
   c. Infections are more frequent after colocystoplasty than ileocystoplasty
   d. About 4% of patients need hospital admission for sepsis
   e. Acute pyelonephritis occurs in 10% to 17% of patients with colon and ileal conduits. It occurs both in the early postoperative period and during the long term.
   f. Approximately 4% of patients with ileal conduits die of sepsis
   g. Deterioration of the upper tracts is more likely when the culture becomes dominant for *Proteus* or *Pseudomonas.*

8) **Stone formation (In kidney and reservoir)**
   a. Persistent infections lead to development of calcium-magnesium-ammonium-phosphate stones.
   b. Risk factors for stone formation:
      i. Hyperchloremic metabolic acidosis
      ii. Preexisting pyelonephritis
      iii. Urinary tract infection with a urea-splitting organism i.e. alkalinization
   c. Incidence of renal stones is 3% to 4% in patients with colon conduits, and 10% to 12% with ileal conduits
   d. With continent cecal reservoirs, incidence of calculi within the reservoir is 20%
   e. Major cause of stone formation in conduits and pouches is a foreign body such as a staple or nonabsorbable suture

9) **Problems of removal of portions of gut**
   a. Nutritional problems: With a significant loss of ileum, vitamin B12 malabsorption occurs which in turns leads to anemia and neurologic abnormalities. Loss of ileum also results in malabsorption of bile salts which causes fatty diarrhea.

  b. Loss of the ileocecal valve may result in reflux of large concentrations of bacteria into the ileum and thus bacterial overgrowth in small bowel. This may result in fat and bile salt malabsorption.
  c. The lack of fat absorption may result in deficiencies of the fat-soluble vitamin A, osteomalacia caused by lack of vitamin D, and complexing of calcium with the fats to form soaps in colon, thus preventing its absorption.
  d. Loss of a significant portion of jejunum may result in malabsorption of fat, calcium, and folic acid

10) **Development of urothelial or intestinal cancer**
  a. Tumors include adenocarcinoma (most common), adenomatous polyps, sarcomas, and urothelial carcinoma
  b. The incidence of cancer development in patients with ureterosigmoidostomy varies between 6% and 29%, with a mean of 11%
  c. In general, there is a 10- to 20-year delay before the cancer manifests
  d. The highest incidence of cancer occurs when the transitional epithelium is juxtaposed to the colonic epithelium and both are bathed by feces

NEUROMECHANICAL

- After the bowel wall has been split on its antimesenteric border (detubularized) and reconfigured, acutely there is a marked interruption of coordinated activity fronts, which over a period of 3 months return to their normal coordinated state.
- This has implications on storage, volume and contractions.

TECHNICAL-SURGICAL

1) **Urinary Fistula**
  a. Typically occurs within first 7 to 10 days postoperatively with an incidence of 3% to 9%
  b. Incidence of urinary intestinal leak is markedly reduced by the use of soft Silastic stents
2) **Stricture**
  a. A urinary intestinal leak may cause periureteral fbrosis and scarring with subsequent stricture formation.
  b. Antirefluxing techniques have a higher incidence of stricture
3) **Stoma related complications**
  a. Stomal prolapse
  b. Parastomal hernia
  c. Stomal stenosis
4) **Wound complications:** Infections/dehiscence/Abscess
5) **Others:** GI bleeding, prolonged ileus or intestinal obstruction

Q2: Complications of orthotopic bladder (ONB)

Early and Late Complications

- **Early complications**
  - Bleeding, thrombotic events, infection, and cardiovascular and pulmonary complications are not directly related to the urinary diversion and do not appear to be different in patients undergoing different types of diversion.
  - Gastrointestinal complications are also common after cystectomy and are at least partially related to bowel anastomosis.
  - Urine leak and ureteral complications are possible with any type of diversion. Urine leaks may be more common in continent diversion than in conduits because of the long suture lines, but with good catheter drainage and properly managed stents and drains these usually resolve with observation alone as long as a urinoma does not form.

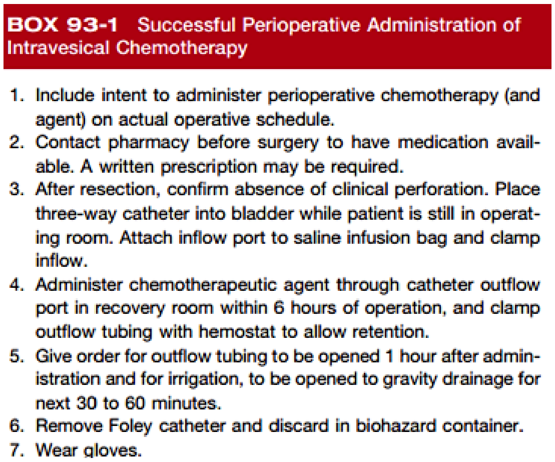
- **Late complications**
  - Incontinence: Day night continence comes first. Night time incontinence remains one of the most bothersome sequelae of neobladders, occurring in 7% to 70% of patients. It results partly from the absence of neurologic feedback, and decreased sphincter tone at night. Nocturnal dieresis also plays a role. Night time incontinence may improve as late as 24 months after surgery. The evaluation and management of urinary incontinence after orthotopic diversion should be delayed until the neobladder has had time to expand. This may take 6 months to a year after surgery

  - Urinary tract infection
  - Ureteroileal or afferent limb obstruction: The direct end-to-side Leadbetter or the combined Wallace anastomoses with interrupted fine absorbable sutures have been shown to have the lowest risk of stricture, approximately 3% to 6%
  - Urethral stricture
  - Upper tract and ONB stones
  - Vaginal fistula
  - ONB rupture or perforation→ This is potentially life threatening complication. Risk is higher in patients with history of radiation therapy.

Other than incontinence, these complications tend to be less common in orthotopic diversion than in continent cutaneous diversion. Many of these can be managed by endoscopic procedures and rarely require open surgical revision.

Q3: Peri-operative intravesical chemotherapy in bladder cancer

- **Rationale**
  - **Floating tumor cells may get implanted immediately after resection and are responsible for many early recurrences**
  - Initial tumors are most commonly found on the floor and lower sidewalls of the bladder, whereas recurrences are often located near the dome as a result of "flotation".
  - Perioperative intravesical chemotherapy is used to kill such cells before implantation
  - A meta-analysis conducted by EORTC showed that a single, immediate instillation of intravesical chemotherapy following TURBT results in a 12% absolute reduction in tumour recurrence (decrease of 39% in odds of recurrence).
- **Agents for perioperative use:** Doxorubicin, epirubicin, pirarubicin, mitomycin-C, thiopeta. Gemcitabine and docetaxel are newer agents.
- **Agents not used perioperatively:** BCG and interferon
  - BCG should never be administered immediately after TURBT because of high the risk of sepsis and death
- **Mitomycin C (MMC)**
  - MMC is an alkylating agent (isolated from *Streptomyces caespitosus)* that inhibits DNA synthesis.
  - MMC is the most effective and most commonly used adjuvant intravesical chemotherapeutic agent perioperatively
  - Usual dose is 40 mg
  - Consistent with its proposed mechanism of action to prevent tumor cell implantation, a single dose administered within 6 hours lessens recurrence rates, whereas a dose 24 hours later does not
  - Maintenance therapy does not reduce the risk further
  - Level 1 data demonstrate clearly that single-dose MMC or epirubicin immediately after resection reduces tumor recurrence; particularly in case of a solitary papillary **low-grade** tumor at initial presentation
  - No benefit has been found in patients with **high-grade** disease.


BOX 93-1 Successful Perioperative Administration of Intravesical Chemotherapy

1. Include intent to administer perioperative chemotherapy (and agent) on actual operative schedule.
2. Contact pharmacy before surgery to have medication available. A written prescription may be required.
3. After resection, confirm absence of clinical perforation. Place three-way catheter into bladder while patient is still in operating room. Attach inflow port to saline infusion bag and clamp inflow.
4. Administer chemotherapeutic agent through catheter outflow port in recovery room within 6 hours of operation, and clamp outflow tubing with hemostat to allow retention.
5. Give order for outflow tubing to be opened 1 hour after administration and for irrigation, to be opened to gravity drainage for next 30 to 60 minutes.
6. Remove Foley catheter and discard in biohazard container.
7. Wear gloves.

  - Limited benefit in for recurrent, multiple tumors
  - NNT to prevent one recurrence in the meta-analysis was 8.5
  - Intravesical chemotherapy may reduce overall cost of care by reducing the need for secondary resections.
  - Optimization of MMC delivery
    - This can reduce recurrence rate by 50%
    - Achieved by emptying the bladder before instillation, using sodium bicarbonate (alkalinisation of urine) to reduce drug degradation, asking anesthetist to keep the patient under-hydarted and avoid diuretics, and increasing concentration of MMC
- Perioperative intravesical therapy has potential problems of cost, complexity, and side effects
- Local irritative symptoms are the most common complications of postoperative instillation, serious sequelae
- Rare deaths have been reported, especially in patients with bladder perforation during resection

- Other reported problems include: chemical cystitis, cutaneous desquamation, decreased bladder capacity as a result of contractures, calcified eschars, and added difficulty and increased complication of subsequent cystectomy.
- **Contraindications:**
    - Extensive resection- plenty of raw area for absorption
    - Bladder perforation

Q4: Blue light cystoscopy

- **Blue light cystoscopy (Fluorescence Cystoscopy)**
    - It involves the use of photoactive porphyrins to diagnose and localize malignant bladder lesions that are impossible to see or clearly distinguish.
    - Endoscopically, malignancy is suspected only on the basis of the presence of visible changes such as tumors or “red spots.” This is obviously a subjective method and has false-positive and false-negative rates of varying degrees. Thus, imperfect sensitivity of cystoscopy potentially explains the high rate of cancer recurrence soon after complete removal of all visible tumors.
    - In blue light cystoscopy, intravesical instillation of 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) is used which is a precursor of photoactive porphyrin. Photoactive porphyrins accumulate preferentially in malignant tissue and they emit red fluorescence when seen under blue light. This can help in diagnosis and better visibility of indiscernible malignant lesions. FC is typically performed by infusing 50mL HAL solution into the bladder for 1 to 3 hours. Bladder is drained 30 minutes prior to any cystoscopic examination. Photoactive porphyrins accumulated in the **neoplastic tissue emit red fluorescence under blue-wavelength light (360-450 nm)** improving the detection of small papillary lesions and CIS. Both rigid and flexible cystoscopy can be performed
    - HAL is a more lipophilic ester, and is the most studied agent. Intravesical HAL for use with fluorescence cystoscopy was approved for use in Europe in 2004.
    - Blue light cystoscopy can detect small papillary tumors and almost one third cases of CIS that are missed on usual white light cystoscopy.
    - Of all tumors, 96% were detected with HAL imaging compared with 77% with standard cystoscopy. A meta-analysis revealed a 20% improved detection rate of NMIBC with FC. However, false positive rate were higher in the FC group.
    - Clinical impact of improved tumor detection lies in fact that this decreases residual tumor rates, decreases recurrence rates and increases recurrence free survival in patients who undergo HAL FC. This impact appears to persist for at least 4 years.
- **Narrow Band Imaging (Blue green cystoscopy)**
    - NBI is a powerful optical image enhancement technology used to improve the visibility of blood vessels inherent to neoplastic processes
    - NBI light is composed of two specific wavelengths that are absorbed by hemoglobin; 415 nm and 540 nm
    - The shorter wavelength in NBI is 415 nm light, which only penetrates the superficial layers of the mucosa. This is absorbed by capillary vessels in the surface of the mucosa and shows up brownish on the video image. This wavelength is particularly useful for detecting tumours, which are often highly vascularised. The second NBI wavelength is 540 nm light, which penetrates deeper than 415 nm light. It is absorbed by blood vessels located deeper within the mucosal layer, and appears cyan on the NBI image. This wavelength allows a better understanding of the vasculature of suspect lesions.
    - Combination of these two allows improved visualization of tumors.
    - Clinical impact of this remains under investigation, and no studies have been performed to date regarding recurrence or progression.
    - Capillaries on the mucosa surface are seen as brown. Veins are in the submucosa and are seen as cyan/blue.

Q5: Adjuvant and neoadjuvant therapy in bladder cancer
ADJUVANT THERAPY

- **Rationale and arguments in-favour**
    - Patients with pT3-T4 or node-positive disease are at high risk for failure or metastasis after RC
    - Adjuvant chemotherapy may be used to treat micrometastatic disease and to improve survival
    - Adjuvant nature of chemotherapy allows for immediate local treatment with cystectomy and avoids any delay
      in treatment in patients with chemotherapy-resistant tumors

  - Availability of final pathology allows selection of patients at the highest risk for failure and thus most likely to benefit, while sparing those who are less likely to progress from the side effects of chemotherapy
- **Limitation and argument against**
  - It is often difficult or impossible for patients to receive chemotherapy following cystectomy because of major surgery, deteriorating renal function, or peri-operative complications.
- Various regimens used include: Cisplatin single agent, CM, CMV, GC, MVAC, MVEC (E- Epirubicin)
- First prospective, RCT to demonstrate a survival benefit with adjuvant chemotherapy was reported by the 'University of Southern California'(USC) group, which included pT3/T4 or N+ patients
- CALGB, EORTC and SWOG trials closed prematurely because of poor accrual.
- Recent most trial "Italian adjuvant chemotherapy, multicenter, phase III RCT"was published in 2012.
  - 194 patients with pT2G3, pT3-4, N0-2 urothelial carcinoma
  - Compared observation (n = 92) versus chemotherapy [GC] (n =102)
  - No statistical difference in disease free survival
  - But, study was underpowered due to smaller sample size
- Advanced Bladder Cancer (ABC) Meta-analysis Collaboration **(2005)** reviewed 11 RCTs and ultimately included 6 trials
  - Total 491 patients
  - Showed 25% relative reduction in the risk of death in favour of adjuvant chemotherapy
  - This translated to 9% absolute survival benefit at 3 years
  - However, evidence was insufficient, as RCTs included in meta-analysis suffered from small sample sizes,
    early closure of trials, limitations in statistical analysis, and differences in the way disease-free survival was defined.
- Updated meta-analysis including 945 patients was reported in **2014**
  - HR for DFS is 0.66 (p = 0.014; 95% CI, 0.48–0.92)
  - Concluded that adjuvant chemotherapy is most beneficial in node-positive disease
  - However, this meta-analysis was also limited by similar issues like the previous one
- Current NCCN guidelines **favour NACT** instead of adjuvant chemotherapy based on higher-level evidence data. However, the guidelines do suggest considering adjuvant chemotherapy in the setting of pT3-4 or N+ disease.
- Current EUA guidelines **recommend** adjuvant chemotherapy within clinical trials but not as a routine, as there is no sufficient evidence to support its routine use.

NEO-ADJUVANT CHEMOTHERAPY (NACT)

- **Rationale**
  - About 50% patients with MIBC treated with cystectomy alone will progress to metastatic disease, indicating that surgery alone is not sufficient treatment in about half of patients with MIBC
  - Cisplatin-based chemotherapy has shown to provide response rates in multiple
- **Arguments in-favour of NACT**
  - Chemotherapy is better tolerated before surgery, rather than after surgery which may result in delay in chemotherapy because of complications or debilitation.
  - Patients presenting with micrometastasis will receive therapy in a more timely fashion when their burden of disease is potentially low.
  - NACT may downstage bulky and locally advanced disease, allowing for more chances of negative surgical
    margins and thus reducing local recurrence after RC
  - NACT allows assessment of response to therapy at each individual patient level

- **Arguments against of NACT**
  - NACT results in delay of definitive local therapy for patients who do not respond to chemotherapy and thus leads to disease progression
- EORTC/MRC (1999) performed the largest NACT trial in bladder cancer
  - Multicenter, RCT with T2-T4aNxM0
  - 491 randomized to NACT with CMV x 3 followed by RC/RT
  - 485 to RC/RT alone
  - Updated results in 2011
    - Significant 16% reduction in the risk of death in NACT arm
    - 6% OS benefit at 10 years [Survival in NACT arm was 36% compared to 30% in the control arm at 10 years]
- Other large trial of NACT was conducted by SWOG
  - Randomized 317 patients to MVAC x 3 followed by RC/RT versus RC alone for cT2-T4aN0M0 disease
  - 14% 5-year OS benefit in NACT arm [57% vs. 43% (*P* = 0.06)]

- Advanced Bladder Cancer (ABC) Meta-analysis Collaboration **(2005)** performed largest meta-analysis on NACT
    - 3005 patients
    - Significant benefit in favour of platinum-based combination NACT in terms of OS (HR = 0.86, 95% CI 0.77 to 0.95).
    - OS benefit of 5%, improving OS from 45% to 50% at 5 years
    - DFS: significant benefit in NACT arm (HR = 0.78, 95% CI 0.71 to 0.86)
    - Pathologic complete response rate of 30% to 40%
- Current NCCN guidelines **recommend**
    - To strongly consider NACT for cT2N0M0 patients
    - Cisplatin-based NACT for cT3-T4aN0M0 patients
- Current EAU guidelines **recommend**
    - Cisplatin-based combination NACT for cT2-T4aN0M0 patients
- Lastly, despite available evidence in support for NACT, it is underused.

Q6: Inverted papilloma bladder

- Inverted papilloma is a benign proliferative lesion, that comprises <1% of all bladder tumors
- Associated with chronic inflammation or bladder outlet obstruction
- Most commonly located on the Trigone, but may be occur throughout the bladder
- It is called inverted because microscopically it shows an inverted growth pattern. This consists of anastomosing islands of normal urothelial cells invaginating from the surface urothelium into the lamina propria.
- Never invaginates into the muscularis propria
- **Lack of cytologic atypia** is one of main defining criteria apart from inverted growth
- Almost always behave in a benign fashion with only a 1% incidence of tumor recurrence
- Transurethral resection is the treatment of choice.
- Occasionally, inverted papillomas are present with coexistent urothelial cancer **elsewhere** in the urinary system, occurring **more commonly in the upper tract than the bladder**.
- Thus, inverted papilloma could be considered a risk factor for urothelial carcinoma, and it is clinically prudent to exclude urothelial carcinoma cancer when it is diagnosed.
- Main D/D is urothelial cancer with an inverted growth pattern which can be differentiated with use fluorescent in-situ hybridization (FISH) to evaluate chromosomal changes.
- Other rarer differentials include nephrogenic adenoma, paraganglioma and carcinoid tumour.
- Follow-up with cystoscopy has been suggested.

Q7: Second TURBT

- **Rationale:**
    - Complete tumor removal is not always possible, which may be because of very large tumor volume, tumor located at anatomic inaccessible or difficult to access sites, medical instability during TURBT requiring premature cessation of resection, or risk of perforation.
    - Even in the absence of these circumstances repeat TUR is often indicated if high-grade tumor is identified because the potential for under-staging high-risk disease ranges from 18% to 37%. This increases to 64% in T1 high risk cases when muscle is absent.
    - Residual tumor is identified at the site of the initial resection in at least 40% of cases on repeat TURBT.
    - Second TURBT may help correcting clinical staging errors in half of those patients.
- Repeat TURBT is usually appropriate in the evaluation of T1 tumors because a repeat TUR can demonstrate worse prognostic findings in up to 25% of specimens. This is especially likely if no muscle is identified on initial pathology, which can occur in almost half of cases.
- Second TURBT may change treatment in 1/3rd of patients.
- In an observational study, survival was 63% in patients who underwent a second TURBT versus 40% for those who did not.
- Recurrences appeared to be lower after repeat TURBT.
- The efficacy of BCG in preventing progression appears to be higher in patients with high-grade papillary tumors and CIS if a restaging TURBT was performed before instillation of BCG.
- Repeat resection is helpful in the setting of a second opinion unless clear evidence of muscle invasion is identified on the initial resection, especially if the outside pathology slides are not available for review.
- **Expert consensus recommends that pT1 and many high-grade Ta tumors merit repeat resection.**
- Timing of second TURBT

  - There is no consensus on timing, but most urologists recommend 1 to 6 weeks after the initial resection
- Collection of separate superficial and deep specimens is not required at second TURBT, unless a new lesion is detected.

Q8: Jejunal conduit syndrome

- Jejunum is used for urinary diversion only when it is inadvisable to use either colon or ileum, because of higher rate of electrolyte derangements.
- Circumstances where jejunum has to be used: Extensive irradiation that involves the ileum, severe adhesions of ileum, absence of large bowel, and absent colon with inflammatory disease of the distal small bowel.
- Contraindications to its use: Severe bowel nutritional disorders and the presence of another acceptable segment
- Early and long-term complications are similar to those for ileal conduit except that the electrolyte abnormality is hyperkalemic, hyponatremic metabolic acidosis instead of the hyperchloremic metabolic acidosis of ileal diversion
- **Jejunal conduit syndrome** comprises of **typical and specific electrolyte abnormalities of hyperkalemic, hyponatremic metabolic acidosis and volume depletion** seen in patients with jejunal diversion.

- **Pathophysiology**
  - This develops because of inherent absorptive properties of jejunum, which result in loss of sodium chloride along with water into the urine passing through the conduit and absorption of potassium and urea from it.

- **Clinical presentation** is usually with dehydration, nausea, vomiting, muscle weakness, fever and lethargy

- **Treatment**
  - Correction of dehydration and acidosis with I/V administration of sodium chloride and sodium bicarbonate which is followed by oral salt supplementation for sometime
  - Thiazide diuretics may also be used to treat hyperkalemia

- **Prevention**
  - Use of smaller jejunal conduit
  - Avoid prolonged I/V hyperalimentation post-operatively

Q9: Hyperchloraemic acidosis (HCA) in Urology

- HCA is also known as non-anion gap metabolic acidosis or normal anion gap metabolic acidosis. This occurs when HCO_3^- is lost from kidneys or GI-tract or both. Cl^- (along with Na^+) is absorbed to keep anion gap normal.

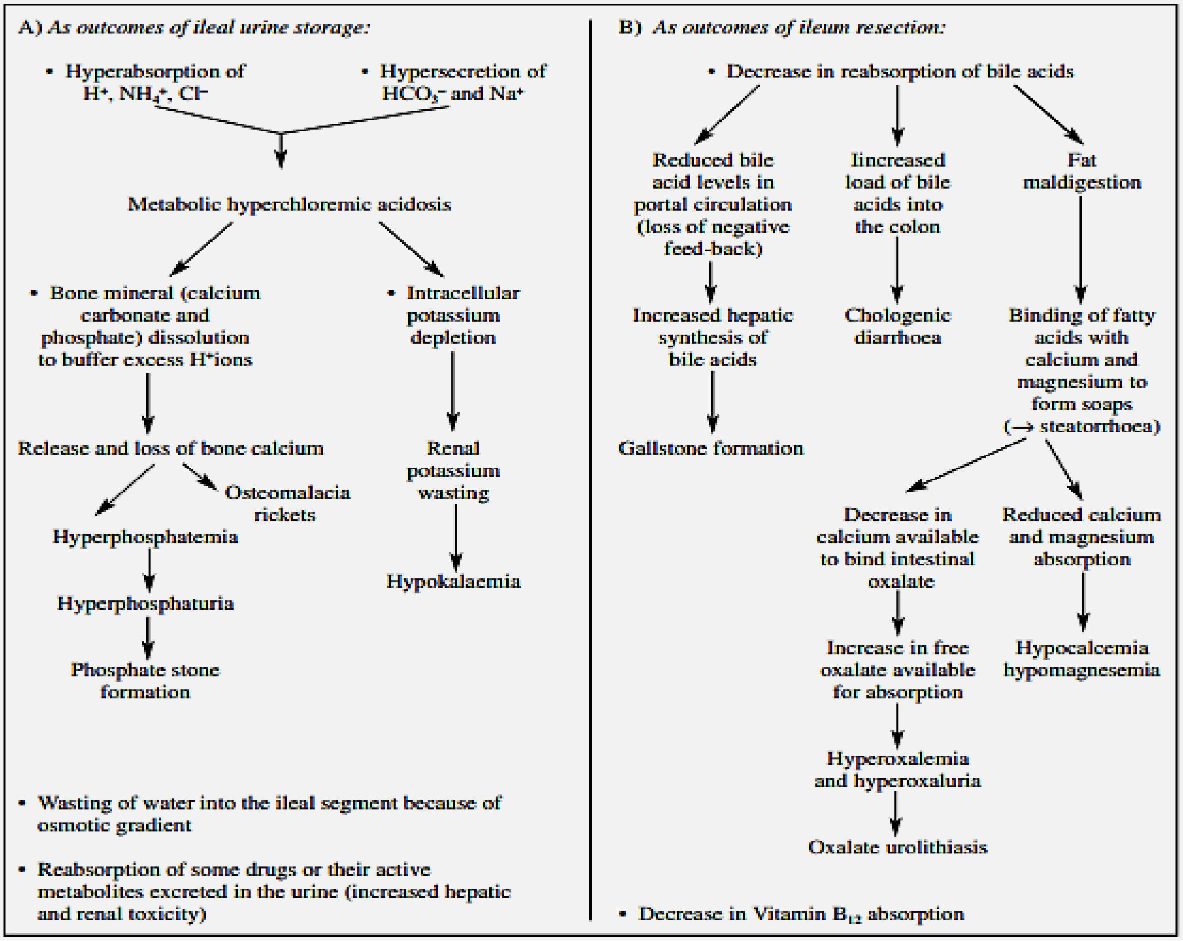
- **Common causes of HCA relevant in urology**
  - Renal impairment/tubular dysfunction
  - RTA Types 1 and 2 (With persistent hypokalemia)
  - Type 4 RTA, Hypo-aldosteronism (associated with hyperkalemia)
  - Urinary intestinal diversion using ileum or colon, and ureterosigmoidostomies
  - Carbonic anhydrase inhibitors, Ammonium chloride administration
- Incidence in ileal conduit is 2-30%

- **Mechanism**
  - Ammonia absorption: NH_4^+ ions dissociate into NH_3 and H^+ in intestinal segment of diversion. NH_3 diffuses into cells and H^+ ion is actively absorbed in exchange for Na^+ sodium. NH_4^+ can also be absorbed in place of K^+ (because chronic intra-cellular acidosis promotes K^+ loss) through potassium channels. On the other hand HCO_3^- is excreted and Cl^- is absorbed in exchange. Hence, $NH_4^+/H^+$and Cl^- are absorbed and Na^+ and HCO_3^- are secreted, thus leading to hyperchloremic acidosis.
  - In RTA-2 there is impaired distal renal tubular secretion of H^+
- It is usually well tolerated, especially with appropriate respiratory compensation. Symptoms include fatigue, anorexia, nausea, weakness

- **Complications of HCA**
  - Bone Metabolism
    - Chronic HCA following urinary diversion is buffered by bone calcium, carbonate and sodium. This results in demineralization of bone.
    - Acidosis also impairs renal activation of vitamin D, which again affects normal bone mineralization.
    - These problems are of more importance in children undergoing urinary diversion with intestine.
  - Calculi
    - Patients with urinary intestinal diversion are at increased risk of stone formation. Among them, those with HCA are most susceptible.
- **Treatment**
  - Alkalinization with oral Na-bicarbonate or citrate (caution in cardiac or renal disease, as they can cause fluid overload due to their Na content)
  - Chlorpromazine or nicotinic acid have been used for acidosis In patients who cannot tolerate excessive Na
  - It is important to check K-levels before bicarbonate therapy as later can worsen hypokalemia
-

**PEARLS

Table I. Main metabolic abnormalities in patients with ileal continent urinary diversion.


A) As outcomes of ileal urine storage:
• Hyperabsorption of H^+, NH_4^+, Cl^-
• Hypersecretion of HCO_3^- and Na^+
Metabolic hyperchloremic acidosis
• Bone mineral (calcium carbonate and phosphate) dissolution to buffer excess H^+ions
• Intracellular potassium depletion
Release and loss of bone calcium
Osteomalacia rickets
Hyperphosphatemia
Hyperphosphaturia
Phosphate stone formation
Renal potassium wasting
Hypokalaemia
• Wasting of water into the ileal segment because of osmotic gradient
• Reabsorption of some drugs or their active metabolites excreted in the urine (increased hepatic and renal toxicity)
B) As outcomes of ileum resection:
• Decrease in reabsorption of bile acids
Reduced bile acid levels in portal circulation (loss of negative feed-back)
Iincreased load of bile acids into the colon
Fat maldigestion
Increased hepatic synthesis of bile acids
Gallstone formation
Chologenic diarrhoea
Binding of fatty acids with calcium and magnesium to form soaps (→ steatorrhoea)
Decrease in calcium available to bind intestinal oxalate
Reduced calcium and magnesium absorption
Increase in free oxalate available for absorption
Hypocalcemia hypomagnesemia
Hyperoxalemia and hyperoxaluria
Oxalate urolithiasis
• Decrease in Vitamin B_{12} absorption

Q10: Early cystectomy in pT1G3- pros and cons

- **Definition of Early cystectomy**
  - Variable
  - Radical cystectomy has been traditionally termed *early cystectomy* when performed before the traditional indication of documented muscle invasion. It is performed for high risk NMIBC.
  - Any cystectomy for NMIBC after TURBT within 1 month to 3/4/24 months
  - Cystectomy in NMIBC without the trial of intravesical therapy
- **Rationale**
  - After initial treatment of NMIBC, regular follow-up and office cystoscopies are required which are invasive and add to the cost of follow-up

  - T1 high-grade has a variable clinical profile with biological behaviour similar to MIBC. There is good evidence to suggest potential to underestimate disease status in **high-risk** patients.
  - High-grade disease has higher chances of finding residual tumor on repeat resection
  - Residual tumor found on repeat resection results in higher chance of development of muscle invasion
  - Problems with TURBT
    - Significant risk of under-staging
    - Residual disease on second TURBT: 27-78% (mean 47%)
    - Upstaging on second TURBT: 2-28% (mean 13%)
    - Presence of detrussor in initial TURBT is the single most important factor that determines upstaging **(14% with and 49% without muscle)**
    - Experience of the surgeon performing the first TURBT
  - Stage progression for high grade NMIBC is 27-63% (53%) compared to 2-12 % for low grade lesions. Thus, despite local therapy, many cases of high-grade NMIBC will progress to MIBC.

  - Mortality of HG T1 is about 33%
  - Further, there is significant drop in 5-year survival from 92% for cT1 (early) to 63% cT2 stage (deferred) with cystectomy
  - For CIS, although the initial response rate to BCG can be >80%, patients fail treatment have 50% chance of disease progression and attendant mortality. Risk of progression increases to 80% after failure of 2nd BCG course.
  - Early BCG failure (within 3-month) for T1 tumors is associated with 82% progression rate, compared with a 25% in patients with late BCG failure (after 3 months)

- **High-risk patients** (include any of the following)
  - T1
  - High grade or G3
  - CIS
  - Multiple, recurrent, large (>3cm) for Ta, G1,G2 lesion (all conditions to be present)
  - Micropapillary variant
- Risk of progression must be weighed against the risk, morbidity, and impact on quality of life for cystectomy. Thus a reasonable goal might be a **"timely" cystectomy** for patients at risk.
  - AUA guidelines listed cystectomy as the first option for patients with refractory high-grade NMIBC after initial course of intravesical therapy.
- **Pros**
  - Allows more accurate pathologic staging for clinical T1 tumors
  - Ten-year DFS of 90% for pT1, compared with 64% of those with cT1 tumors but found to have MIBC at RC
  - Multiple studies have shown reduced survival in patients with HG NMIBC with delayed RC
  - Half of high-grade presumed NMIBC were found to be MIBC when subjected to RC
  - Surveillance for high-risk NMIBC patients creates a false sense of security on disease control status as these patients on surveillance when develop progression to muscle invasion may have poorer prognosis than those who have MIBC on initial presentation. This can be avoided by early cyctectomy.
- **Cons**
  - Perioperative mortality of 1-6% with RC
  - Urinary and sexual dysfunction
  - Complications related to use of bowel
  - Psychological trauma of not having native intact bladder
  - About 1/4th of patients with high-risk NMIBC treated with aggressive intravesical therapy would survive with
    an intact, functioning native bladder at 15 years.
  - Another 1/4th will otherwise do well and die of causes other than bladder cancer

- **Prognostic factors in NMIBC**
  - Patient related
    - Older age
    - Female gender
  - Surgical
    - >3 cm
    - Multifocal
    - Recurrent/ residual
    - Prostatic involvement
    - Multiple TURT/ deferred cystectomy

    - Pathological
        - CIS
        - LVI
        - Increased depth of LP invasion
        - Extensive LP involvement
        - Variant histology

- **Numbers**
    - pT1 high grade: 6-23%
    - Upstaging after 2nd TURBT: 14% (detrussor+), 49% (detrussor-)
    - Residual disease after 2nd TURT: 27-78%
    - BCG:
        - 30-60% will recur
        - 15-30% will progress
    - Early cystectomy:
        - 10-60% will upstage
        - 75-88% 5 year CSS
        - <3% surgical mortality

- **In the era of restaging TURBT, indications for immediate cystectomy** following initial TURBT for HGT1 tumors should be one or more of the following
    - No evidence of extravesical disease on cross-sectional imaging performed at the most 8 weeks before cystectomy, in whom restaging TUR will not change management
    - Endoscopically unresectable disease
    - Patient preference
    - Poorly functioning bladder in a patient who will not tolerate intravesical therapy
    - Multiple poor prognostic factors in a patient in whom restaging TURBT will not change management (i.e. potentially identify eligibility for NACT)
    - HGT1 tumor in a diverticulum

Q11: Tumour markers in Ca-bladder or Urinary markers of urothelial cancer (UC) of bladder

- Tumor marker based tests have been developed in an attempt to replace or support urinary cytology.
- Current urinary markers are based on detection of either of
    - Tumor-associated antigens
    - Blood group antigens
    - Growth factors
    - Cell cycle and apoptosis
    - Extracellular matrix proteins

- **Available tumor markers**
    1. **BTA stat (**qualitative, point-of-care test) **BTA TRAK** (quantitative)
        - Detect human complement factor H–related protein
        - Sensitivity 50% to 80%
        - Specificity 50% to 75%
        - More sensitive than cytology
        - Falsely positive: inflammation, infection, or hematuria

    2. **ImmunoCyt**
        - Hybrid of cytology and an immune-fluorescence assay
        - Three fluorescent labelled mAb are targeted at a urothelial cancer variant of carcinoembryonic antigen (CEA) and two bladder mucins
        - Sensitivity 86%
        - Specificity 79%
        - Not affected by benign conditions, but interpretation is complex and operator dependent

    3. **NMP22 BladderChek**
        - Detects nuclear matrix protein 22 (NMP22) which is part of mitotic apparatus
        - NMP22 is elevated in UC, but it is also released from dead and dying urothelial cells
        - False positive: Benign conditions e.g. stones, infection, inflammation, hematuria, and even manipulations like cystoscopy
        - Available as both quantitative, laboratory-based immunoassay and a qualitative point-of-care test

- Sensitivity 68.5% to 88.5%
- Specificity 65.2% to 91.3%
- Multi-institutional trial:
  - Overall, NMP22 was more sensitive than cytology but less specific
  - Sensitivity: 50% for NMIBC and 90% MIBC
  - Overall sensitivity of 55.7%
  - Overall specificity 85.7% [For cytology 99.2%]
  - NMP22 increased the sensitivity of cystoscopy from 88.6% to 93.7%

4. **UroVysion**
   - Cytology-based test that uses FISH of DNA probes to detect certain chromosomal foci
   - Specific DNA probes are used to identify aneuploidy of Ch. 3, 7, and 17 combined 9p21 locus. This combination of probes has the best sensitivity and specificity.
   - **Sensitivity** increases with the grade and stage of tumor

Grade	**Cytology**	**FISH/UroVysion**
1	19%	58%
2	50%	77%
3	71%	96%

Stage	**Cytology**	**FISH/UroVysion**
Ta	35%	64%
T1	66%	83%
T2/ MIBC	76%	94%

   - In comparative studies, cytology detected only 67% of CIS versus 100% detected by FISH
   - **Plus points**
     - **UroVysion has the highest specificity of the available tumor markers**
     - It detects chromosomal changes before the clinical development of malignancy, which usually leads to identification of clinical tumors within 3-15 months after initial positive UroVysion in majority of cases.
     - May allow risk stratification of patients for recurrence, and thus help to individualize surveillance protocols, as patients with NMIBC with negative UroVysion on follow up are unlikely to have recurrence within next 1 year.
     - Clarify equivocal findings of atypical or negative cytology
     - Not affected by hematuria, inflammation, or other factors, thus it can be a useful marker of BCG response

- **Limitations of current tumor markers for UC of bladder**
  1. Most of these tests have good sensitivity but poor specificity, thus have high false-positive rates. High specificity is required to limit the number of negative biopsies. Therefore, further diagnostic tests are anyway required in case of positive results.
  2. Complex interpretation
  3. Lack of prospective data to support their impact on prognosis or disease management
  4. Thus, not in wide spread practice
  5. Usefulness and choice of a particular tumor marker test is to use is not clear at this time

Q12: Management of SCC bladder

- **SCC Bladder:** Rare, 2%-5% of all bladder malignancies. Two subtypes
  1. **Non-bilharzial type**
     - Occurs in Western countries and represents < 5% of bladder tumors
     - Mainly in 7th decade and slight male preponderance
     - Main predisposing factor→ prolonged indwelling urethral catheter in patients with SCI (incidence <1%)
     - Main symptom is haematuria
     - Usually diagnosed at an advanced stage and most are of moderate and high grades
     - Predominantly ulcerative and involving the trigone and lateral walls
     - Lymph node metastasis is infrequent (8-10%), but prognosis is generally poor
     - Radical cystectomy provides the best treatment
     - Outcome can be improved by early detection with frequent cytology, cystoscopy and biopsy in suspected SCI patients

2. **Bilharzial type**
    - Occurs commonly in Middle East, South-east Asia and South America where schistosomiasis (*Schistosoma hematobium)* is endemic
    - Diagnosed in 5th decade, and 5 times commoner in men
    - Carcinogenesis occurs due to chronic inflammation because of parasite, as well as bacterial and viral infections that are commonly associated with bilharzial infestation. Also, nitrosamine is generated in very high levels in the urine of patients chronically infected with *Schistosoma.*
    - Main clinical presentation is with irritative bladder symptoms and hematuria
    - Although most tumours are of low and moderate grades, many patients present at advanced stage
    - Predominantly nodular and usually arise from upper half of bladder
    - Lymph-node metastasis occurs in about 1/5th of patients
    - Radical cystectomy remains the main treatment. Prognosis is better than that of non-bilharzial type
    - With RC, 5-year survival rate of 50%

- **Management**
    - External radiation therapy alone→ reported results are uniformly poor
    - Radical cystectomy with standard pelvic lymphadenectomy is the standard treatment
    - Preoperative irradiation followed by cystectomy may have additional survival advantage. Five year survival with this approach is 34-50%. Because of rarity of SCC bladder, it is difficult to conduct well controlled prospective studies on the role of RT.
    - Survival correlates with stage, grade and lymph node metastasis. LN metastasis reduces survival by half.
    - SCC is a chemotherapy-resistant tumour, and currently no chemotherapy programme has yet been found to be effective against metastatic SCC. Gem-Cis, and Epirubicin have been tried as NACT.
    - Most important is prevention and early detection. Bilharzial bladder cancer is a good example of a preventable malignant disease.

Q13: Intravesical BCG

- **Intravesical therapy:** Two groups of intravesical therapeutic agents are available.
    - Immunotherapeutic agents: BCG, Interferon
    - Chemotherapeutic agents: Most commonly used include Mitomycin C, Doxorubicin (Adriamycin), Gemcitabine, Thiotepa
- **Intravesical BCG**
    - BCG is a live attenuated vaccine (developed from Mycobacterium bovis) for tuberculosis that has shown antitumor activity in UC. BCG remains the most effective intravesical treatment for NMIBC.
    - Introduced as a treatment for urothelial bladder cancer about 40 years ago by Morales. Original regimen described by Morales included a percutaneous dose which was discontinued after success with a similar intravesical regimen.
    - Indicated for high grade NMIBC (TaHG, T1HG, and CIS) to reduce recurrence and progression.
    - BCG is the only agent know to reduce progression
    - TURBT followed by intravesical BCG has been proven to be superior to TURBT alone, and to TURBT plus intravesical chemotherapy for delaying recurrence.
    - Reduction in recurrence and progression= 30-40%
    - Response to BCG at 6 months can be used as a predictor of prognosis
- **Strains (**current view is that available stains do not differ in efficacy)
    - Danish 1331 (2-6 x 10^8 CFU/ml)
    - Frappier (Was used by Morales)
    - Pasteur
    - Japanese
    - Connaught
    - Tice

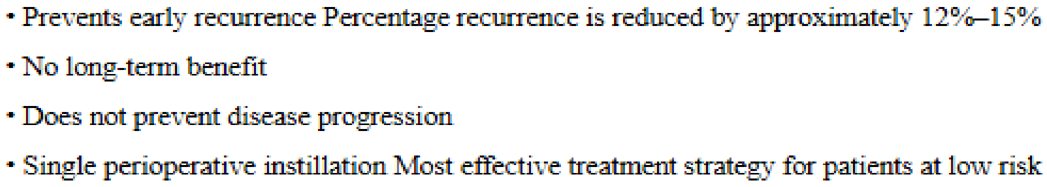
- **Administration**
  - Typically instillations are started 2 to 4 weeks after TURBT. Urinalysis is performed immediately before instillation to confirm absence of infection or significant bleeding. BCG powdered vaccine is reconstituted with 50 mL of saline and administered through a urethral catheter under gravity. Bladder is emptied before instillation. After instillation, patient should retain the solution for at least 2 hours. Some Practice of asking the patient turn from side to side is not evidence based. Fluid, diuretic, and caffeine restriction before instillation limits dilution of the agent by urine and facilitates adequate retention of the agent for 2 hours.
  - Quinolones may affect the viability of BCG and should be avoided during the course of BCG

- **Contraindications**
  - Absolute
    - Immediately after TURBT
    - Traumatic catheterization (delay for several days to 1 week)
    - Gross hematuria
    - Personal H/O BCG sepsis
    - Total incontinence
  - Relative
    - Active UTI (intravasation risk)
    - Liver disease (Isoniazid cannot be given if sepsis occurs)
    - Personal history of tuberculosis
    - Poor overall performance status
    - HIV, immunosuppression (EAU 2017)
    - Advanced age

- **Mechanism of action of BCG**
  - After instillation, the initial step is direct binding of mycobacteria to **fibronectin** in the bladder wall, followed by massive cell-mediated local immunological and an antiangiogenic response
  - Various cytokines involved in initiation or maintenance of inflammatory immune process include TNF-α, GM-CSF, IFN-γ, and IL 1,2,5,6,8,10,12, and 18. Most important of these appear to **IFN-γ, IL-2, and IL-12 which lead to induction of T-helper type-1 cells.** This immunologic response activates cell-mediated cytotoxic mechanisms that are responsible for efficacy of BCG.
  - Response to intravesical BCG may be limited if a patient has an immunosuppressive disease
  - Urinary cytokine levels peak at 3rd week after an induction course

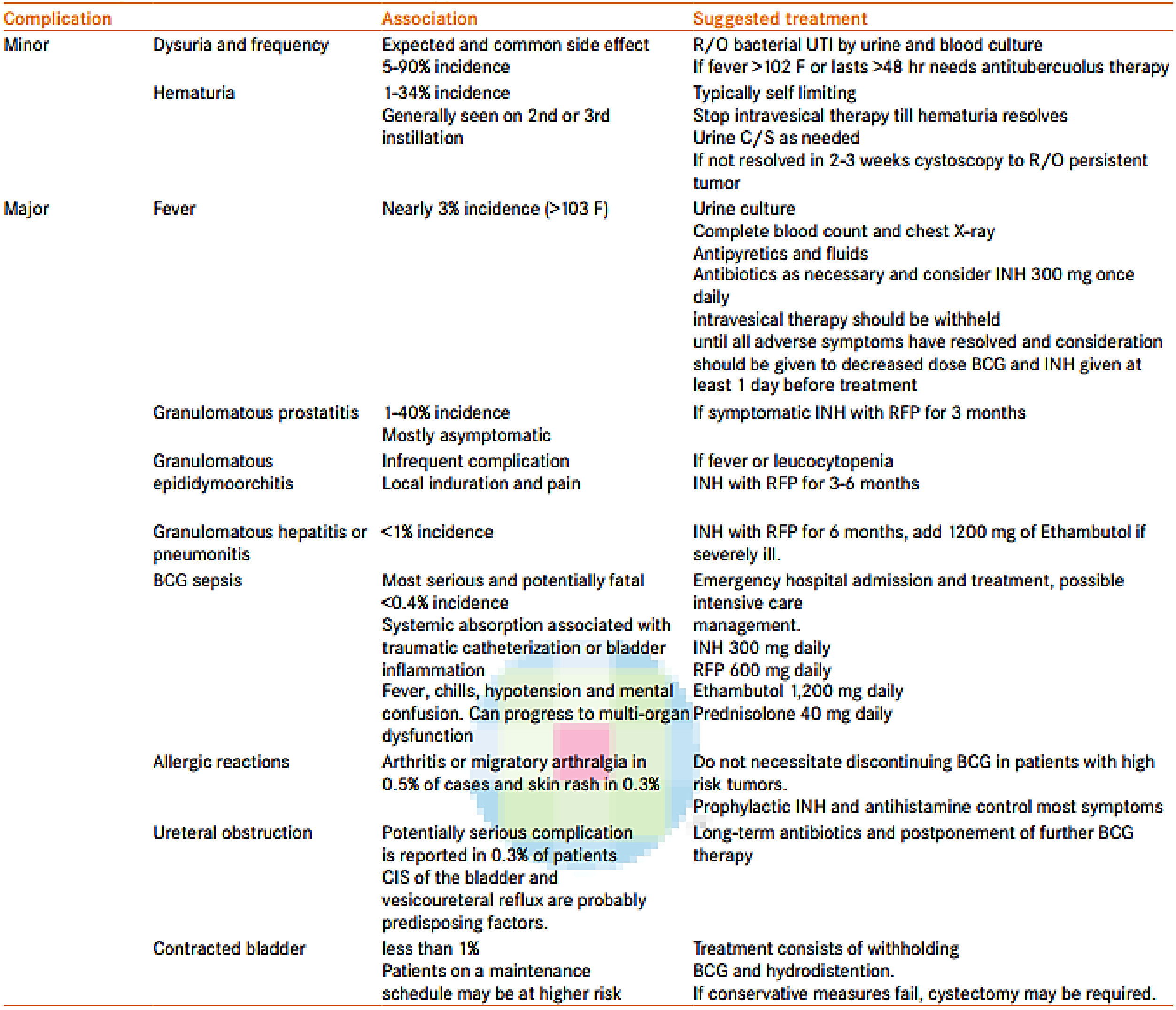
- **Optimum dose and schedule**
  - Standard dose was 120 mg (Frappier); however, in an effort to reduce the toxicity dose reduction has been proposed. Danish 40 mg has been found to be equally effective.
  - Induction course consists of six weekly instillations.
  - Maintenance is typically given as three weekly instillations at 3 and 6 months and then every 6 months for up to 3 years. At least a year of maintenance is recommended by EAU and AUA for low and intermediate risk cases. For high risk cases maintenance should be given for 3 years.
  - **Repeat/2nd induction course**
    - Indicated in cases of BCG recurrence and persistence of CIS
    - Additional response to a 2nd induction course is 25%-30%
    - Additional BCG for refractory disease after second 6-week induction course is NOT recommended because this is associated with significant risk of progression (20% to 50%)

- **Chracteristics of intravesical chemotherapy**



- Prevents early recurrence Percentage recurrence is reduced by approximately 12%–15%
- No long-term benefit
- Does not prevent disease progression
- Single perioperative instillation Most effective treatment strategy for patients at low risk

- **Complications of intravesical BCG therapy and management**
  - Intravesical BCG is associated with more side effects than intravesical chemotherapy. However, serious side effects occur in <5% of patients and can be treated effectively in almost all cases.



Complication		Association	Suggested treatment
Minor	Dysuria and frequency	Expected and common side effect 5-90% incidence	R/O bacterial UTI by urine and blood culture If fever >102 F or lasts >48 hr needs antitubercuolus therapy
	Hematuria	1-34% incidence Generally seen on 2nd or 3rd instillation	Typically self limiting Stop intravesical therapy till hematuria resolves Urine C/S as needed If not resolved in 2-3 weeks cystoscopy to R/O persistent tumor
Major	Fever	Nearly 3% incidence (>103 F)	Urine culture Complete blood count and chest X-ray Antipyretics and fluids Antibiotics as necessary and consider INH 300 mg once daily intravesical therapy should be withheld until all adverse symptoms have resolved and consideration should be given to decreased dose BCG and INH given at least 1 day before treatment
	Granulomatous prostatitis	1-40% incidence Mostly asymptomatic	If symptomatic INH with RFP for 3 months
	Granulomatous epididymoorchitis	Infrequent complication Local induration and pain	If fever or leucocytopenia INH with RFP for 3-6 months
	Granulomatous hepatitis or pneumonitis	<1% incidence	INH with RFP for 6 months, add 1200 mg of Ethambutol if severely ill.
	BCG sepsis	Most serious and potentially fatal <0.4% incidence Systemic absorption associated with traumatic catheterization or bladder inflammation Fever, chills, hypotension and mental confusion. Can progress to multi-organ dysfunction	Emergency hospital admission and treatment, possible intensive care management. INH 300 mg daily RFP 600 mg daily Ethambutol 1,200 mg daily Prednisolone 40 mg daily
	Allergic reactions	Arthritis or migratory arthralgia in 0.5% of cases and skin rash in 0.3%	Do not necessitate discontinuing BCG in patients with high risk tumors. Prophylactic INH and antihistamine control most symptoms
	Ureteral obstruction	Potentially serious complication is reported in 0.3% of patients CIS of the bladder and vesicoureteral reflux are probably predisposing factors.	Long-term antibiotics and postponement of further BCG therapy
	Contracted bladder	less than 1% Patients on a maintenance schedule may be at higher risk	Treatment consists of withholding BCG and hydrodistention. If conservative measures fail, cystectomy may be required.

Numbers and brief literature

1. **BCG for CIS**
   - Initial tumor-free response rate is 84%
   - 50% durable response for median period of 4 years
   - 30% remain free of tumor progression or recurrence at 10 years
   - Progression rate is 20% of initial responders at 5 years but is 95% in non-responders
   - AUA guidelines supported BCG as the preferred initial treatment option for CIS
2. **BCG for Residual Tumor**
   - Effective to treat small residual papillary lesions but should not be used as a substitute for surgical resection
   - Nearly 60% response by residual tumor has been demonstrated with BCG alone
3. **BCG to Prevent Recurrence**
   - Approximately 30%-40% decreased tumor recurrence with 6-week course of BCG
   - Maintenance BCG reduces the recurrences further
   - Efficacy of BCG after TURBT for high-risk papillary T1 lesions: Recurrence rates of 16%-40% and progression rates of 4.4% to 40%
   - 40% still experience recurrence in 5 years

4. **Impact of BCG on Progression**
   - In CIS, BCG reduced the risk of progression by 35%
   - Cystectomy rate was significantly decreased for CIS patients treated with BCG (11% vs. 55%), as was the time to cystectomy
   - Long-term survival advantage is not fully defined

Q14: Optical coherence tomography (OCT) in bladder cancer

- **Principle and Instrumentation of OCT**
    - OCT is an emerging novel imaging technology which enables cross-sectional imaging of tissue microstructure in-situ and in real-time. OCT is analogous to USG imaging, except that imaging is performed by measuring optical scattering of light rather than sound.
    - Resolution is one to two orders higher than that of USG. OCT can achieve 1-10 µm resolutions and 1-2 mm penetration depths, approaching those of standard excisional biopsy and histopathology, but without the need to remove and process tissue specimens.
    - OCT imaging can be performed fiber-optically using hand-held probes, endoscopes, catheters, laparoscopes, and needles in non-invasive or minimally-invasive manners.
    - Currently OCT probes are based on fiberoptics and have a diameter of 2.7 mm, so they pass through the working channel of standard cystoscopes. It uses near-infrared light waves.
    - 3D-OCT imaging is also feasible
- In urology, OCT has been found applications in bladder, ureter, and kidney

- **OCT in bladder cancer**
    - Single-spot evaluation takes only 1.5 s, which makes the technique ideal as an adjunct to HAL cystoscopy (Blue light)
    - In urinary bladder, it offers a near-cellular level evaluation of the superficial layers of the wall, which enables urothelium, lamina propria, and muscularis propria to be distinguished. This property provides OCT with high sensitivity and specificity in identifying malignant changes with sensitivity and specificity ranging from 84-100% and 78-90% respectively. This can reduce the sampling errors and false-positivity of biopsies
    - OCT can discriminate Ta, T1, and T2 tumors in real-time. MIBC can be detected with 100% sensitivity.
    - OCT is also a viable option for follow up surveillance of NMIBC, and for monitoring of therapy
    - Valuable imaging in situations where biopsy may be hazardous or impossible
- **Limitations of OCT**
    - OCT has ability to differentiate between scarring and UC, but inflammation or scarring may still cause false-positives interpretation
    - Size of the probe limits the field of view, thus OCT is not suitable for bladder mapping
    - In large or broad-based tumors imaging of depth is impaired, thus making staging inaccurate
    - Need of separate light source that produces near-infrared light

Q15: Bladder preservation protocols

- **Goal and principles**
    - Goal f bladder preservation protocols in invasive bladder cancer (MIBC) should be curative and maintenance of functionally intact bladder
    - Historically bladder preservation using any single modality therapy (radical TURBT, chemotherapy alone, or radiation alone) has poorer results compared to that of RC. Therefore, successful bladder preservation is based on **multimodal therapy** involving **aggressive TURBT, systemic chemotherapy, and radiation therapy**.

- **Patient selection**
    - Appropriate patient selection is extremely important to optimize response to bladder-sparing protocols. Patients who are unfit for surgery or who refuse surgery can be considered for bladder preservation.
    - Fit patients should be offered RC as the standard of care; however, bladder preservation is a reasonable option for highly selected and appropriately counselled patients.
    - Criteria for or Ideal candidates for any bladder preservation protocol
        - Good baseline bladder function
        - No residual tumor at the resection site on repeat TURBT
        - Normal examination under anesthesia
        - Normal upper urinary tracts
        - No urethral involvement
        - < 3 cm lesion
        - Lack of multifocal disease
        - N0 disease
    - If strict selection criteria (mentioned above) are followed approximately 6% to 19% of patients presenting with MIBC could be considered as candidates for bladder preservation.
    - Contraindications
        - Fit patient with MIBC willing for RC

        - Presence of hydronephrosis
        - Obvious T3 disease on imaging
        - CIS
        - Multifocal tumors
        - Grossly incomplete TURBT

- **Single Modality Treatment**

1. **Radical TURBT**
    - About 10% of patients with T2 disease found on TURBT will have pT0 disease when subjected to radical cystectomy alone. This suggests that aggressive TURBT can be curative in small number of patients. However these are the patients who have disease which is clinically <T2 but found to be focal pT2 on TURBT specimen, and re-staging TURBT shows either no tumor or non-invasive residual tumor.
    - In highly selected patients, reasonable long-term results have been reported. The 5- and 10-year DFS survival rates are about 80% and 75% with actual bladder preservation rates of 65% and 55%, respectively.
    - This approach requires intensive endoscopic surveillance every 3 months for 2 years, every 6 months for 3 years, and annually thereafter.
    - Patients with CIS at initial TURBT should be treated with intravesical therapy. Also, repeat wide resection of TURBT site is performed at 3-6 months.
    - Major limitation of radical TURBT monotherapy is the significant risk of occult extravesical disease noted in patients with clinical T2 disease. pT3 and pT4 disease is found in cT2 on RC in up to 40% and 9%, respectively. Additionally, there is about 25% risk of occult nodal metastasis at the time of surgery. Therefore, TUR monotherapy would be undertreatment in about 50% of patients presenting with MIBC.

2. **Partial Cystectomy**
    - Advantages of partial cystectomy over radical TURBT
        - Pelvic lymphadenectomy can be performed, that allows for complete staging
        - Full thickness of bladder wall and associated perivesical fat can be removed.
    - Problems of partial cystectomy
        - High rates of local recurrence and wound recurrences
        - Historically poor outcomes
    - Ideal candidates for partial cystectomy
        - Small, solitary tumors amenable to wide resection with 2-cm margins
        - Tumor should be away from the ureteral orifices
        - Location of the tumor should allow for complete resection while maintaining adequate functional bladder capacity.
        - Partial cystectomy is contraindicated in the presence of CIS
    - The 5-year OS and DFS are 67%-70% and 84%-87%, respectively.

3. **Radiation Monotherapy**
    - Radiation therapy for MIBC (with or without debulking TURBT) is typically administered in 1.5 to 2.0 Gy dose per fractions with total dose of 55-65 Gy.
    - Five-year and 10-year OS is 26%-50% and 20% respectively.
    - Local recurrences occur in >30% of cases.
    - **These results are poorer to those of combined chemoradiation regimens.**
    - Patients with multifocal tumors, HDN, and higher clinical T stage are poor candidates for radiation monotherapy.
    - Combined EBRT and brachytherapy have also been explored as possible bladder preservation protocols
    - Radiation monotherapy currently can be considered in the palliative setting or for patients who are otherwise unfit and unwilling to undergo any other form of therapy (chemotherapy or surgery).

4. **Primary Chemotherapy**
    - Similar to radiation monotherapy, combination chemoradiation is superior to chemotherapy alone.
    - Some data suggest that a few patients with low-risk MIBC can be cured with TUR and chemotherapy alone.
    - These data come from series of NACT followed by RC

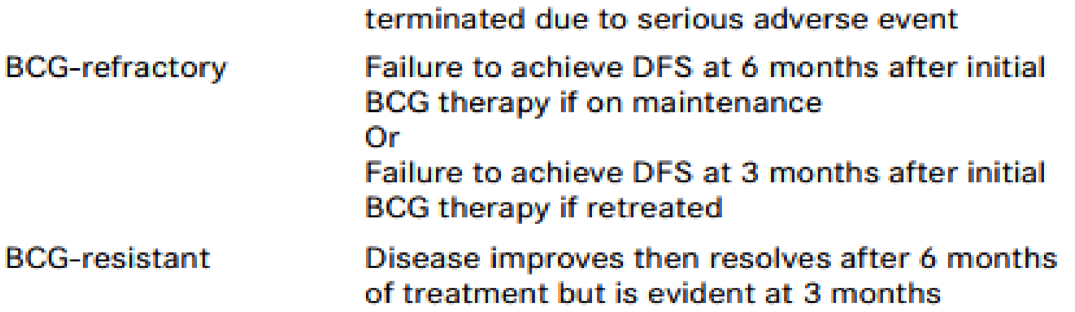
- **Trimodal Therapy for bladder cancer (TURBT + Chemoradiation)**
    - Approximately 6% to 19% of patients presenting with MIBC could be considered for bladder preservation if strict selection criteria are followed.

- Maximal tumor debulking with aggressive TURBT is critical part of trimodal therapy. OS at 5 and 10 years are significantly improved for patients with complete TURBT versus without complete resection (57% and 39% versus 43% and 29%)

- Following TURBT, the two basic strategies for trimodal bladder preservation include
  - Split-course:
    - Patients are given induction chemoradiation therapy to approximately 40 Gy, which is followed by restaging with cross-sectional imaging and endoscopic evaluation **(mid-treatment restaging)**. If persistent invasive disease is noted, RC is recommended.
    - If no persistent invasive disease is found, chemoradiation is completed to about 64 Gy of total dose.
    - Chemotherapy regimens used include cisplatin/paclitaxel or cisplatin/5-fluorouracil
  - Continuous-course:
    - Full course of chemoradiation is delivered, followed by restaging 6 months after completion of therapy to allow time for an adequate response to therapy.
    - Chemotherapy regimens used in this setting include MMC followed by 5-FU (in conjunction with radiation) and cisplatin-based combination chemotherapy. Five-year OS is 48%-54%. Overall 5-year bladder-intact survival is 40% to 54%.

Q16: Management of BCG failure, or Newer intravesical agents/modalities for BCG refractory bladder cancer (essay)

- **Terminology**



BCG-relapsing	Recurrence after achieving 6 months of DFS
BCG-intolerant	Less than adequate course of therapy terminated due to serious adverse event
BCG-refractory	Failure to achieve DFS at 6 months after initial BCG therapy if on maintenance Or Failure to achieve DFS at 3 months after initial BCG therapy if retreated
BCG-resistant	Disease improves then resolves after 6 months of treatment but is evident at 3 months

- **Recurrence and failure after intravesical BCG** (Categories of unsuccessful treatment with intravesical BCG)

BCG failure

I. Whenever a MIBC is detected during follow-up

II. **BCG-refractory**

(1). If **high-grade**, NMIBC (papillary) is present at 3 months **of start of BCG** [Further conservative treatment with BCG has increased risk of progression]

(2). If **CIS (without concomitant papillary tumour)** is present at both 3 and 6 months **of start of BCG** [CIS found at 3 months→ an additional BCG course can achieve a complete response in > 50%]

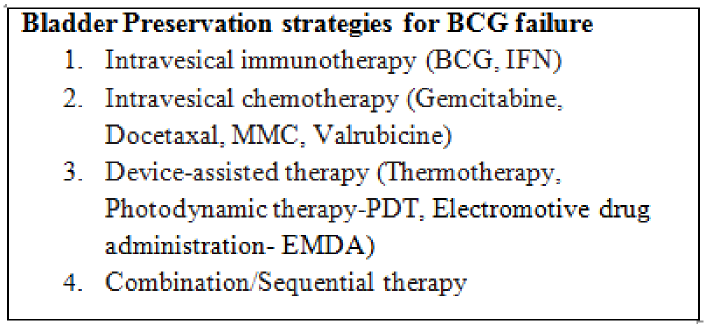
(3). If **high-grade** NMIBC appears **during** BCG therapy [Low-grade recurrence during or after BCG treatment are not considered as BCG failure]

III. **High-grade** recurrence **after completion of BCG maintenance** despite an initial response

BCG intolerance

Severe side effects that prevent further BCG instillation before completing treatment

- **Management of failed BCG include has two broad options:**
    - Immediate Radical Cystectomy
    - Further Bladder Preservation strategies



Bladder Preservation strategies for BCG failure

1. Intravesical immunotherapy (BCG, IFN)
2. Intravesical chemotherapy (Gemcitabine, Docetaxal, MMC, Valrubicine)
3. Device-assisted therapy (Thermotherapy, Photodynamic therapy-PDT, Electromotive drug administration- EMDA)
4. Combination/Sequential therapy

I. Immediate Radical Cystectomy

- RC is the standard of care and the treatment of choice for CIS failing adequate BCG and as an option in other high-risk tumours. RC in superficial tumours that failed BCG provides high tumour-specific survival rates of 80%-90% at 5 years.
- Immediate RC this setting has been shown to improve DFS, life expectancy, and quality of life and decreases overall cost of treatment.
- However, RC is a major surgery with associated significant procedure related morbidity and mortality (2-6%). Further, patient population is the one with advanced age and multiple comorbidites. This must be considered when deciding treatment.

II. Bladder Preservation strategies for BCG failure

- Treatments other than RC must be considered oncologically inferior in patients with BCG failure. However, these options are valid for patients unfit for RC, and those refusing for RC.

1) Intrvesical immunotherapy

a. **Further BCG:** In patients who have persistent disease at 3 months, a further course of BCG may provide complete response in more than 50% of cases, both in CIS and papillary tumours. However, further courses of BCG (beyond two) are not recommended because of the reduced chance of success of < 20% and high progression rates of >50%.

b. **Interferon (IFN-α):** IFN-α is a naturally occurring cell-signalling cytokine that is produced by immune system in response to insults such as tumour cell growth. Long-term success rate of IFN-α monotherapy for BCG failure is generally under 15%. It is reported that combination IFN-α + BCG is a reasonable salvage option if BCG failure occurs >1 year after BCG treatment. On the other hand those with BCG failure occurring < 1 year of start of BCG or more BCG failures, are not candidates for conservative therapies.

2) Intravesical Chemotherapy

a. **Gemcitabine (GC):** GC is a nucleotide analogue and thus inhibits DNA synthesis. GC is now a standard first-line systemic chemotherapeutic agent used in NACT setting and palliative treatment of UC. Intravesical use of GC has been reported in BCG failures. A 2012 Cochrane review concluded "The available evidence suggests that intravesical GC may have a role in the management of intermediate-risk patients, as an alternate choice to MMC in previously treated patients with recurrent disease and in high-risk BGC-refractory patients with NMIBC." However, at present its efficacy, impact on preventing or delaying disease progression and overall survival is not clear.

b. **Docetaxel:** Belongs to the taxane group of chemotherapy agents, and act by inhibition of microtubule depolymerization, leading to cell cycle arrest and cell death. Complete response to docetaxel in BCG-refractory NMIBC has been reported as high as (55-75%). Maintenance therapy is important.

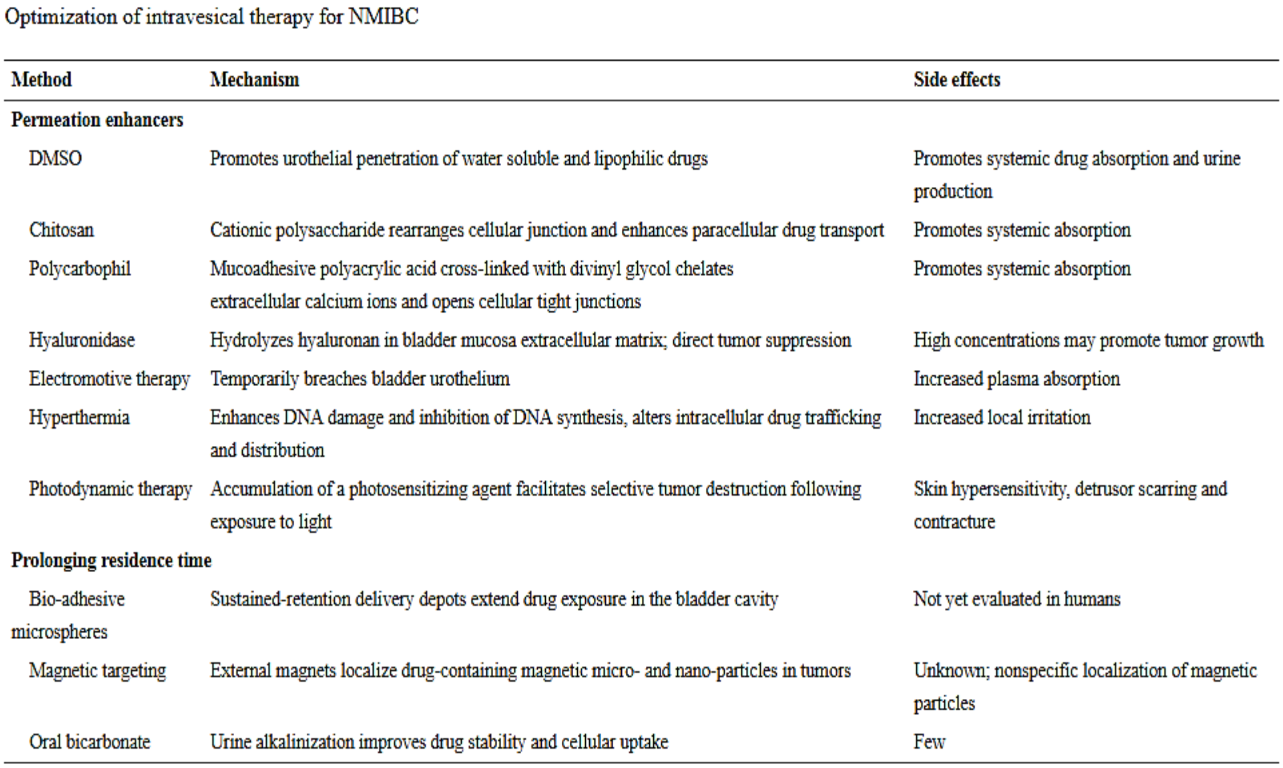
c. **Valrubicin:** Valrubicin is a semisynthetic derivative of anthracycline antibiotic doxorubicin (adriamycin) which acts by intercalating DNA. It has been shown to benefit patients with BCG-refractory CIS. In this setting, reported complete response is 21%. Other anthracyclines that have been used are **doxorubicin and epirubicin**.

d. **Mitomycin C (MMC):** Only a few studies have reported treatment of BCG failure with subsequent intravesical MMC. Intravesical MMC combined with bladder wall hyperthermia has been shown to be better than MMC alone.

e. **Thiotepa**: An alkylating agent that inhibits nucleic acid synthesis by inducing the cross-linkage of DNA, RNA, and proteins. It is currently the only chemotherapeutic agent approved by FDA for papillary TCC.

3) **Device assisted therapy**
   a. **Thermo-chemotherapy (TC) or Synergo System**: Combination of intravesical MMC and bladder wall hyperthermia is termed TC. Bladder wall is heated to temperatures of ≈ 42C using a thermocouple-monitored catheter and microwave equipment with sequential administration of intravesical MMC. This has been found to be superior to conventional MMC alone in high-risk patients, by providing 59% relative reduction in NMIBC recurrence compared with MMC alone.
   b. **Photodynamic therapy (PDT):** Bladder cancer cells are photosensitized by giving oral 5-aminolaevulinic acid. Photosensitized cancer cells are then excited with a specific wavelength of intravesical light, leading to their destruction. Experience is that of small number of patients with rapidly recurring, multifocal BCG-refractory high-risk NMIBC.
   c. **Electromotive drug administration (EMDA):** This technique uses current gradient between the drug and the bladder wall to enhance transmembrane transport of intravesical chemotherapy agents. EMDA-MMC is equal to BCG in terms of recurrence rate in BCG-naïve high-risk NMIBC and significantly better than passive standard MMC. There are no studies of EMDA in patients specifically with ‘BCG failure’.

4) **Combination / Sequential Therapy**
   Various regimens include
   a. MMC and BCG
   b. Combined BCG/IFN-α
   c. BCG and EMDA-MMC
   d. MMC and Gemcitabine
   e. PDT and BCG



Optimization of intravesical therapy for NMIBC

Method	Mechanism	Side effects
Permeation enhancers		
DMSO	Promotes urothelial penetration of water soluble and lipophilic drugs	Promotes systemic drug absorption and urine production
Chitosan	Cationic polysaccharide rearranges cellular junction and enhances paracellular drug transport	Promotes systemic absorption
Polycarbophil	Mucoadhesive polyacrylic acid cross-linked with divinyl glycol chelates extracellular calcium ions and opens cellular tight junctions	Promotes systemic absorption
Hyaluronidase	Hydrolyzes hyaluronan in bladder mucosa extracellular matrix; direct tumor suppression	High concentrations may promote tumor growth
Electromotive therapy	Temporarily breaches bladder urothelium	Increased plasma absorption
Hyperthermia	Enhances DNA damage and inhibition of DNA synthesis, alters intracellular drug trafficking and distribution	Increased local irritation
Photodynamic therapy	Accumulation of a photosensitizing agent facilitates selective tumor destruction following exposure to light	Skin hypersensitivity, detrusor scarring and contracture
Prolonging residence time		
Bio-adhesive microspheres	Sustained-retention delivery depots extend drug exposure in the bladder cavity	Not yet evaluated in humans
Magnetic targeting	External magnets localize drug-containing magnetic micro- and nano-particles in tumors	Unknown; nonspecific localization of magnetic particles
Oral bicarbonate	Urine alkalinization improves drug stability and cellular uptake	Few

Q17: CIS- Clinical features and management

- **Definition:** CIS is defined as a **flat, noninvasive** urothelial cancer which is **high-grade** and is regarded as a precursor to the development of invasive high-grade cancer. S**evere dysplasia or severe atypia are also regarded as same entity as CIS.**
- De novo CIS constitutes less than 3% of all urothelial neoplasms; however, CIS detected concurrently or secondarily during follow-up of urothelial carcinoma constitutes 45% and 90%, respectively, of bladder cancer.
- **From 40% to 83% of patients with CIS will develop MIBC if untreated. 20% of** patients thought to have CIS alone and subjected RC are found to invasion on final pathology. For T1 lesions undergoing RC, risk of upstaging is 55% if there was associated CIS compared with 6% if no CIS.
- **Clinical features:**
    - Irritative **bladder symptoms** such as dysuria, frequency, or urgency with or without hematuria are common presentation.

- **Management of CIS bladder**
  - Treatment strategy: CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG or RC. DFS rates after immediate RC for CIS are excellent (about 90%), but as many as 40-50% of patients might be over treated.

  - **Treatment options**

Intravesical therapies	Surgical
First line • BCG	**Radical cystectomy**
Second line • Valrubicin • MMC • BCG+IFNα • Gemcitabine • Docetaxel/Paclitaxel • EMDA-MMC • TC-MMC • GC+MMC • Mycobacterial cell wall nucleic acid (MCNA) complex	

  - **Intravesical BCG for CIS**
    - Initial tumor-free response rate is 84% (versus 48% with intravesical chemotherapy)
    - 50% durable response for median period of 4 years
    - 30% remain free of tumor progression or recurrence at 10 years.
    - BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different
      immunotherapy. Progression rate is 20% of initial responders at 5 years but is 95% in non-responders
    - AUA guidelines supported BCG as the preferred initial treatment option for CIS
    - A meta-analysis has shown 59% risk reduction of BCG failure compared with intavesical chemotherapy for patients with CIS.
    - To summarize: Compared to intravesical chemotherapy, BCG treatment of CIS increases the complete response rate, DFS, and reduces the risk of tumour progression.
  - **Other Intravesical agents** as mentioned above
  - **Radical cystectomy**
    - RC is accepted as a second-line therapy for CIS after intravesical BCG
    - Immediate RC may have higher survival rates when compared to delayed RC after failed BCG
    - However, RC is a major surgery with associated significant procedure related morbidity and mortality (2-6%). Further, patient population is the one with advanced age and multiple comorbidites. This must be considered when deciding treatment.

1. TRUS in Urology

Most common imaging modality for the prostate.

- Most commonly used for prostate cancer detection, also used in the evaluation of other conditions such as infertility
- Directing the biopsy of prostate cancer, the role of staging localized prostate cancer using TRUS is very limited
- Commercially available endorectal probes are available in both **side- and end-fire** models and transmit frequencies of 6 to 10 MHz.
- Most modern ultrasound machines have optimized self programming for TRUS and biopsy.
- Newer biplane probes provide simultaneous sagittal and transverse imaging modes. Probes provide a scanning angle approaching 180 degrees to allow simultaneous visualization of the entire gland in both the transverse and sagittal planes.
- Increasing frequency yields increased resolution. As the frequency of the probe is increased, the portion of the image that is in focus (*focal range*) is closer to the transducer
- The commonly used **7-MHz transducer** produces a high-resolution image with a focal range from 1 to 4 cm from the transducer (best for PZ where most cancers arise).
- Lower frequency transducers (e.g., older 4-MHz transducers) have a focal range from 2 to 8 cm but at lower resolution. Lower frequency transducers improve anterior delineation of large glands, increasing the accuracy of volume measurements, but provide poor internal architecture visualization.
- Ultrasound energy does not propagate through air. For this reason, a water-density substance, termed a ***coupling medium,*** is used. The coupling medium, usually sonographic jelly or lubricant, is placed between the probe and the rectal surface.
- If the probe is covered with a protective condom, the coupling medium is placed between the probe and the condom, as well as between the condom and the rectal surface.

Techniques

The complete TRUS evaluation of the prostate includes scanning in both the sagittal and transverse planes to obtain a volume calculation. The CZ and PZ are inspected for hypoechoic lesions and contour abnormalities, and the SVs and vasa deferentia are fully visualized.

Machine Settings

- The image magnification is adjusted so that most of the prostate is visible without the image being too small to allow detection of abnormalities. In general, the magnification is low during prostate measurements so that the entire gland is seen.
- During biopsies, magnification is maximal for visualization of needle passage.
- The optimal brightness setting results in a **medium-gray image of the normal PZ.** This gray tone serves as the reference point for judging lesions as hypoechoic (darker than the normal PZ), isoechoic (similar to the normal PZ), hyperechoic (lighter than the normal PZ), or anechoic (completely black).

Probe Manipulation

Patients are typically scanned in the left lateral decubitus position Performed in both the transverse and the sagittal planes.

There are two approaches to probe manipulation for transverse / sagittal imaging

Volume Calculations

- Prostate volume can be calculated through a variety of formulas. Volume calculation requires measurement of up to three prostate dimensions.
- In the axial plane, **the transverse and anteroposterior (AP) dimensions** are measured at the point of widest transverse diameter
- The **longitudinal dimension** is measured in the sagittal plane just off the midline, because the bladder neck may obscure the cephalad extent of the gland
- Most formulas assume that the gland conforms to an ideal geometric shape:
  - either an ellipse = (π/6 × transverse diameter × AP diameter × longitudinal diameter)
  - sphere = (π/6 × transverse diameter3)
  - prolate = (egg-shaped)
  - spheroid = (π/6 × transverse diameter2 × AP diameter)
- The mature average prostate is between 20 and 25 g and remains relatively constant until about age 50, when the gland enlarges in many men. When a more accurate determination of gland volume is required, such as during brachytherapy, planimetry may be employed.
- With the patient in the lithotomy position, the probe is mounted to a stepping device, and **serial transverse images are obtained at set intervals (e.g., 3 to 5 mm)** through the entire length of the gland.

Cystic Lesions of the Prostate

1) Cystic prostatic structures are common on TRUS.
   - Simple cysts -- Thin walled, anechoic, and show acoustic enhancement posterior to the cyst.
   - Congenital prostatic cystic lesions may arise from either
   - Müllerian (müllerian duct cysts and prostatic utricles) or
   - Wolffian (ejaculatory duct and seminal vesicle cysts) structures.

2) An enlarged prostatic utricle represents a diverticular projection from the posterior urethra at the level of the verumontanum and appears as a midline anechoic structure.
3) These are associated with genital anomalies, including hypospadias (most common), ambiguous genitalia, undescended testes, and congenital urethral polyps
4) Müllerian duct cysts also appear as midline anechoic lesions that result from failure of the müllerian ducts to fuse with the urethra. They are generally ovoid to pear shaped with the cyst neck oriented toward the verumontanum. When müllerian duct cysts are present, men should be evaluated for unilateral renal agenesis
5) Lateral paraprostatic cystic structures include seminal vesicle and vas deferens cysts (wolffian in origin).
6) Ejaculatory duct cysts are typically small, lie off of the midline, and may accompany ejaculatory duct obstruction / obliteration with azoospermia
7) Seminal vesicle cysts can be caused by congenital or acquired obstruction of the ejaculatory duct and are associated with cystic renal disease; Up to two thirds of men with seminal vesicle cysts may also have renal agenesis
8) Acquired cysts of the TZ result from hemorrhagic degeneration of BPH nodules whereas those of the outer gland have no proven etiology.

Prostate Cancer Imaging on TRUS

- **All hypoechoic lesions** within the PZ should be noted and included in the biopsy material
- The lack of a distinct hypoechoic focus does not preclude proceeding with biopsy, because
- **39% of all cancers are isoechoic and up to 1% of tumors may be hyperechoic** on conventional gray-scale TRUS . Other disease processes, such as granulomatous prostatitis, prostatic Infarct, and lymphoma may all produce hypoechoic lesions.

- TZ BPH nodules are typically hypoechoic but may contain isoechoic or even hyperechoic foci. A hypoechoic lesion is malignant in 17% to 57% of cases highlighting the need to biopsy these lesions but recognizing they are not pathognomonic for cancer as once thought.
- Any focal contour abnormalities along the outer edge of the gland and any asymmetries in echotexture from the PZ of one lobe to that of the other are noted.
- Extracapsular extension of prostate cancer, although not well visualized if present as a microfocus, is suggested by a focal loss of the typically bright white periprostatic fat.

TRUS Appearance after Treatment

In general, TRUS findings correlate poorly with pathologic findings and outcomes in irradiated prostates.

- **External- beam radiation** therapy typically decreases volume by 6 months after treatment. Irradiated prostates are diffusely hypoechoic, with poorly defined anatomy. Large hypoechoic tumors, particularly those not responding to therapy, show little change in echogenicity once irradiated, but smaller foci responding well to therapy tend to become isoechoic
- **With interstitial brachytherapy**, there is initial postimplantation edema followed by long-term changes as with external-beam radiation therapy. With an ideal permanent implant, seeds should be distributed evenly throughout the gland. These seeds are **hyperechoic** and demonstrate posterior shadowing.
- **Androgen ablation with luteinizing hormone**– releasing hormone (LHRH) analogs will cause an **average 30% volume decrease** with androgen deprivation in prostates with and without cancer. Volume decreases by approximately 21% at 6 months using agents such as finasteride
- **Postradical prostatectomy** -- TRUS is considered normal if there is **smooth tapering of the bladder neck to the urethra .** Many patients demonstrate a nodule of tissue anterior to the anastomosis, representing the ligated dorsal vein complex Any other hyperechoic or hypoechoic lesions or interruptions of the retro anastomotic fat plane are considered suspicious. Hypoechoic lesions have been reported in 75% to 95% of patients with locally recurrent cancer, Color Doppler has been used to improve cancer detection in the prostatic fossa .

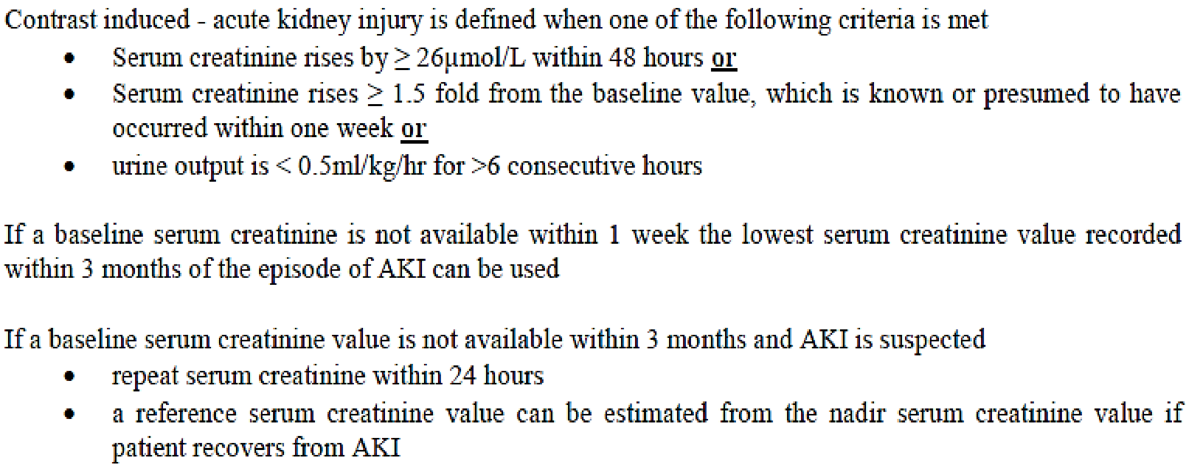
Patients with detectable PSA who are candidates for salvage radiation therapy were once considered for routine biopsy of the anastomotic area. Biopsy of the anastomotic region with PSA recurrence in the absence of a palpable nodule is not usually informative . However, biopsy of an abnormality seen on TRUS, even with a normal digital rectal exam (DRE), can be diagnostic of locally recurrent disease

TRUS and Other Malignancies

- Prostatic involvement with transitional cell carcinoma (TCC) from the bladder is generally not detectable by TRUS. **71% of prostatic stromal TCC lesions are hypoechoic. .** Prostatic TCC detected by TRUS must be confirmed by biopsy, because granulomas resulting from instillation of bacille Calmette-Guérin are common in**.** TCC patients and are also hypoechoic
- Extension to the prostate from the bladder, or urethral squamous cell carcinoma (SCC), is much ore common than is primary prostatic SCC.
- Prostatic SCC appears as an irregular, anterior mass demonstrating relative **hyperechogenicity**
- Adenoid cystic / basal cell carcinoma of the prostate -- Numerous cystic glands -- **multiple, evenly distributed, small, anechoic cysts**
- Prostatic sarcoma is a rare complication of prostatic irradiation, and the TRUS appearance is typified by an irregular, **hypoechoic mass with an anechoic area consistent with necrosis** . Echogenicity of rhabdomyosarcoma is similar to that of normal prostate tissue.
- Hematologic and lymphoid malignancies involving the prostate are generally not visualized with TRUS . Biopsies may demonstrate a lymphocytic infiltrate, but this is often attributed to chronic inflammation if no suspicion of nonprostate malignancy exists.

2. Contrast induced nephropathy

Contrast-induced nephropathy(CIN) is defined as -



Contrast induced - acute kidney injury is defined when one of the following criteria is met

- Serum creatinine rises by ≥ 26µmol/L within 48 hours **or**
- Serum creatinine rises ≥ 1.5 fold from the baseline value, which is known or presumed to have occurred within one week **or**
- urine output is < 0.5ml/kg/hr for >6 consecutive hours

If a baseline serum creatinine is not available within 1 week the lowest serum creatinine value recorded within 3 months of the episode of AKI can be used

If a baseline serum creatinine value is not available within 3 months and AKI is suspected

- repeat serum creatinine within 24 hours
- a reference serum creatinine value can be estimated from the nadir serum creatinine value if patient recovers from AKI

The precise cause of CIN continues to elude investigators but is believed to be a combination of tubular injury and renal ischemia .

High doses of IRCM can impair renal function in some patients for 3 to 5 days

CIN is the third most common cause of acute kidney failure in the hospitalized patients

The most common patient-related risk factors are

- chronic kidney disease (creatinine clearance<60 mL/min),
- diabetes mellitus,
- dehydration,
- congestive heart failure,
- older age (> 75 years old)
- hypertension,
- low hematocrit,
- nephrotoxic medication
    - aminoglycosides
    - NSAIDs
    - Amphotericin B
- ventricular ejection fraction less than 40%.

The patients at highest risk for developing CIN are those with both diabetes *and* preexisting renal insufficiency.

The most common non–patient-related causes are

- High osmolar contrast agents,
- ionic contrast,
- increased contrast viscosity, and
- large-contrast volume infusion

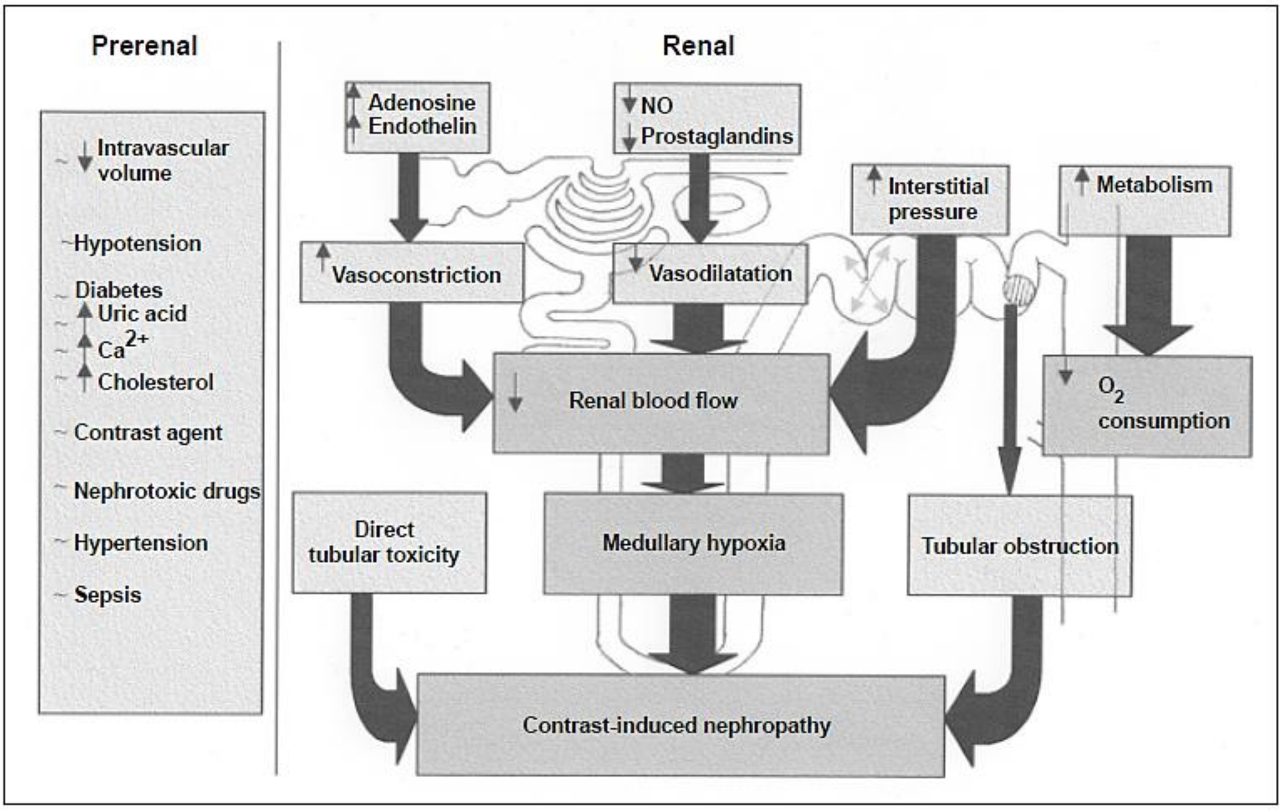


Fig. 1.—Diagram shows proposed pathophysiologic mechanisms of contrast-induced nephropathy. NO = nitric oxide.

The summary of the meta-analysis for the preventionof CIN after contrast media use supports using hydration,bicarbonate, iso- or low-osmolar contrast media, andN-acetylcysteine.

In one review article, N-acetylcysteinewas determined to be more protective than hydrationalone. N-acetylcysteine is inexpensive, readily available, administeredorally, and associated with few drug interactions or side effects. Its mechanism of protection against CIN is not understood but mayserve as a scavenger of oxygen-free radicals and/or augment thevasodilatory effects of nitric oxide .

Doses used in the different studies ranged from 600 to 1200 mg orally twice a day for 2 doses before the contrastenhanced study and 2 doses after the procedure.

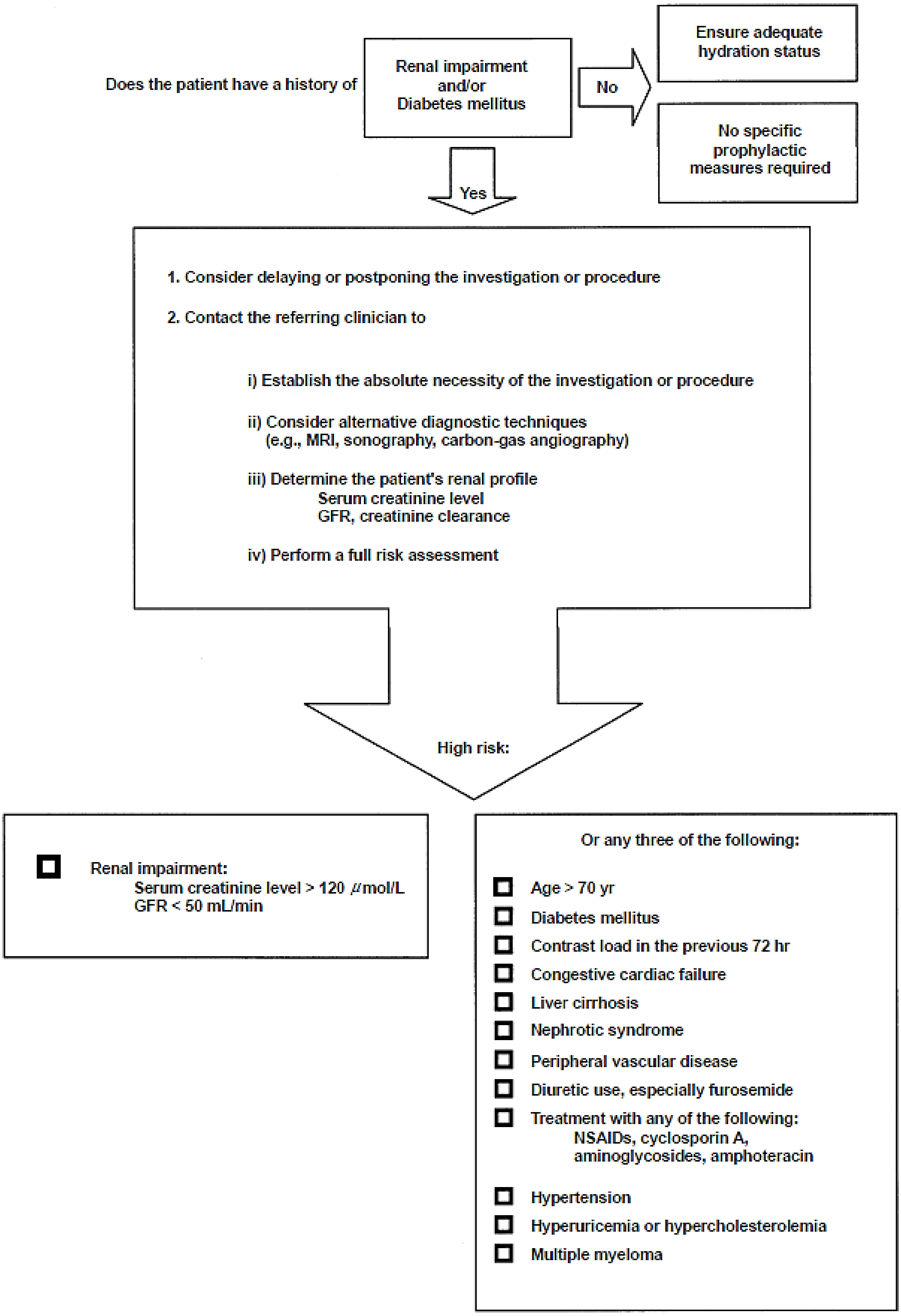

Does the patient have a history of
Renal impairment and/or Diabetes mellitus
No
Ensure adequate hydration status
No specific prophylactic measures required
Yes
1. Consider delaying or postponing the investigation or procedure
2. Contact the referring clinician to
i) Establish the absolute necessity of the investigation or procedure
ii) Consider alternative diagnostic techniques (e.g., MRI, sonography, carbon-gas angiography)
iii) Determine the patient's renal profile
Serum creatinine level
GFR, creatinine clearance
iv) Perform a full risk assessment
High risk:
☐ Renal impairment:
Serum creatinine level > 120 µmol/L
GFR < 50 mL/min
Or any three of the following:
☐ Age > 70 yr
☐ Diabetes mellitus
☐ Contrast load in the previous 72 hr
☐ Congestive cardiac failure
☐ Liver cirrhosis
☐ Nephrotic syndrome
☐ Peripheral vascular disease
☐ Diuretic use, especially furosemide
☐ Treatment with any of the following:
NSAIDs, cyclosporin A, aminoglycosides, amphoteracin
☐ Hypertension
☐ Hyperuricemia or hypercholesterolemia
☐ Multiple myeloma

Fig. 2.—Diagram shows proposed radiology department protocol for prevention of contrast-induced nephropathy. Maximum risk is renal impairment, diabetes, and other risk factors. High risk is renal impairment, diabetes only, and three or more cumulative risk factors. Low risk is less than three risk factors. GFR = glomerular filtration rate, NSAIDs = nonsteroidal antiinflammatory drugs.

3. CT Angio in Urology

Renal Artery Stenosis

- Spiral CT technology imaging of the renal arteries using thin (2-mm) slices during the arterial phase of contrast material injection is performed while the patient holds a single breath.
- Three-dimensional reconstruction of the axial image is then carried out, showing the abdominal aorta with its main branches.
- Atherosclerotic disease affecting the aorta and the renal arteries can be visualized, as well as renal morphology and parenchymal lesions.
- Spiral CTA lacks the ability to define disease distal to the main stem renal artery, and a relatively large volume of intravenous (IV) iodinated contrast material is required to perform the study;
- Advantages of cost, convenience, and widespread availability
- Modern CT technology can also be used to perform virtual endoscopy,which can be helpful for evaluating renal artery stenoses and positioning arterial stents
- Multiple detector–row CT angiography is a new method of CT angiography more accurate depiction of the renal and other visceral arteries

UPJ Obstruction -Spiral CT angiography in failed endopyelotomy, to rule out a crossing vessel. If a significant vessel is found, repeat endopyelotomy is generally not recommended

Angiomyolipoma- CT-angiography ***aneurysmal dilation is found in 50% of angiomyolipomas*** . The size of the aneurysms has been reported to correlate with the risk of rupture

Renal cell carcinoma

- Before partial nephrectomy, evaluation of patients with renal cortical tumors should include imaging to identify locally extensive or metastatic disease.
- Preoperative imaging should also delineate relevant regional anatomy, intrarenal anatomy, and vasculature to minimize blood loss and damage to adjacent renal parenchyma
- Non invasive 3D CT angiography, offers excellent anatomic detail. 3D CT integrates information from arteriography, venography, excretory urography, and conventional two-dimensional CT in to a single imaging modality
- In addition to tumor staging, 3D reconstructions of contrast enhanced CT angiograms, are useful for planning site and extent of planned resection and to determine proximity to the renal hilum, intrarenal vasculature, and collecting system
- 3D CT accurately demonstrates involvement of the collecting system by tumor

TRAUMA-INDUCED RENAL VASCULAR HYPERTENSION

- Suspected traumatic hypertension, evaluation with radiographic studies (CT angiography), to rule out an ***arteriovenous fistula or a pseudoaneurysm*** as the source of the hypertension

- **Donor Work up Pre-Transplant**

4. Captopril scan/ single dose captopril test

Radionuclide renography without ACE inhibition has limited use for the functional or anatomic diagnosis of renovascular disease.

Physiologic principle -- Loss of preferential vasoconstriction of the efferent arteriole that is mediated by AII which maintains the glomerular pressure gradient in cases of RAS. This loss of postglomerular pressure results in a decreased GFR of the kidney distal to the stenosis, which is measured noninvasively by radionuclide renography.

TECHNIQUE:

- The study is performed in well-hydrated patients on liberal salt intake.
- ACE inhibitors are discontinued for 3 to 5 days before the study, but other antihypertensives may be continued.Oral hydration is continued on the day of the procedure.
- **Oral captopril (25 to 50 mg) is usually used, although IV enalapril (0.04 mg/kg) can be used as well .** The captopril renogram is obtained 1 hour after the captopril dose. The use of furosemide has also been suggested to improve the accuracy of ACE renography
- **Optimal radionuclide agents:**
  - Technetium 99m (99mTc)–diethylenetriaminepentaacetic acid (DTPA)
  - Iodine 131 (131I)–orthoiodohippurate (OIH)
  - 99mTc-mercaptoacetyltriglycine (MAG3).
- The imaging characteristics of 99mTc compounds are better than that of 131I compounds.
- On the other hand, OIH and MAG3 are excreted by both glomerular filtration and tubular secretion, whereas DTPA is excreted by glomerular filtration only, making it less optimal for patients with renal dysfunction.
- To date, 99mTc-MAG3 has shown the best results for captopril renography, especially in patients with impaired renal function

INTERPRETATION

Captopril renographic diagnostic criteria have not been well standardized. Criteria suggested by the Consensus Panel on Captopril Renography

Two categories of information are used: **Asymmetry of renal size and function as suggested by the scintigraphic images**

Specific captopril-induced changes in the renogram.

- Delayed time to maximal activity (>11 minutes),
- Significant asymmetry of peak activity of each kidney
- Marked cortical retention of radionuclide
- Marked decrease in the GFR of the ipsilateral kidney.

For radionuclides with tubular excretion (131I-OIH and 99mTc-MAG3), the ratio of 20-minute counts to peak counts can also be used. Normally less than 0.3, a 0.15 change is considered significant.

A small poorly functioning (30%) kidney that shows no change after ACE inhibition, as well as bilateral symmetrical change after ACE inhibition, is considered to be moderately indicative of RVH.

Sensitivity - Approximately 90% to 93% & Specificity - Approximately 93% to 98%

Captopril renography is predictive of a cure or improvement in blood pressure after revascularization in 80% to 90% of cases

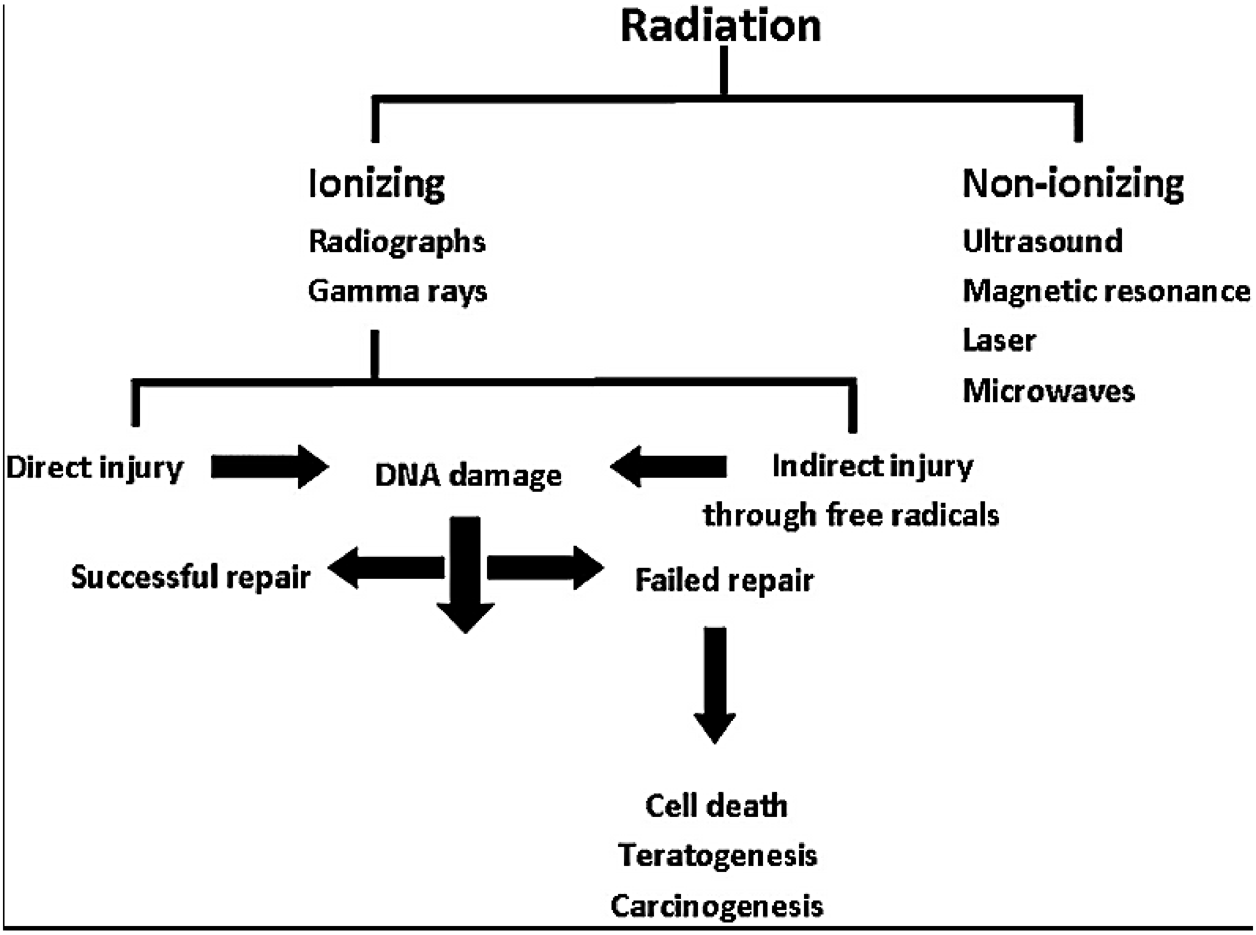
- The presence of bilateral renal artery stenosis,
- Renal artery stenosis to a solitary kidney, or
- Impaired renal function (serum creatinine level > 2.5 to 3 mg/dL) decreases the accuracy of captopril renography.

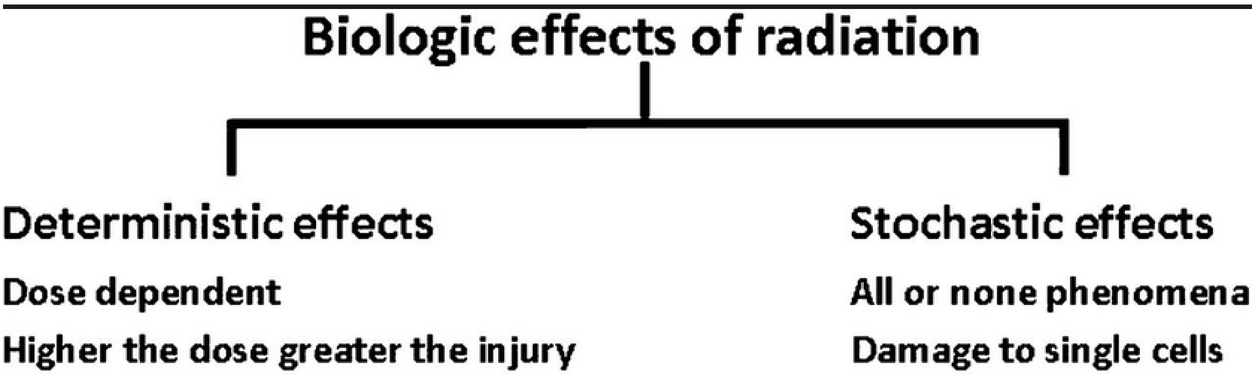
5. Radiation safety

Radiation is the emission or transmission of energy in the form of waves or particles through space or through medium.

Biological effects of radiation-

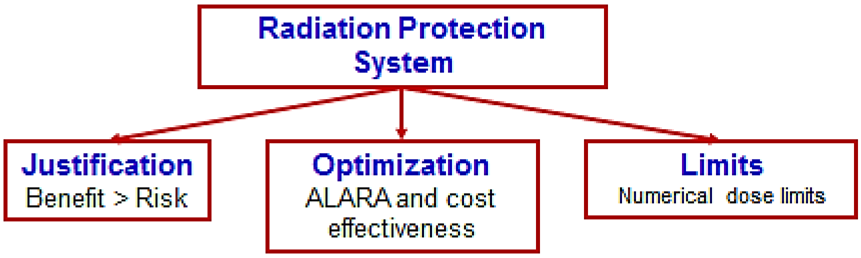
- Direct Action-Photon ejects an electron which produce a biological damage on the DNA
- Indirect Action- Electrons produce highly reactive free radicals which break chemical bonds and produce chemical changes thus biological damage.
- Ionizing radiation-deposits energy that injures or destroys cells; Damages their genetic material (DNA) makes it impossible for these cells to grow.





PRINCIPLES OF RADIATION PROTECTION

The system of radiation protection recommended by the ICRP in Publication 60 is based on three major principles *justification*, *optimization*, and *dose limitation*



Radiation Protection System

Justification
Benefit > Risk

Optimization
ALARA and cost effectiveness

Limits
Numerical dose limits

An effective radiological protection system should use the three principles to ensure that all radiation doses are kept as low as possible

ALARA - As low as reasonably achievable

THREE KEY FACTORS FOR RADIATION PROTECTION-

Be TIME conscious

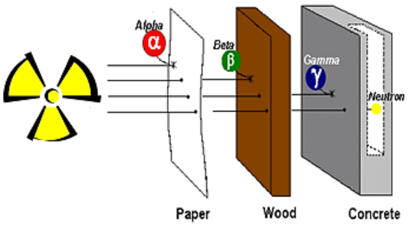
THREE KEY FACTORS FOR RADIATION PROTECTION

BE TIME CONSCIOUS

- Keep the working time in the radiation area to as minimum as possible
- Do not linger in areas of known exposure
- Absorbed dose is proportional to time of exposure ($D \propto t$)

- *Lesser the time you spend in a radiation area, lesser is the dose received - half the time half the dose!*

USE EFFECTIVE SHIELDING

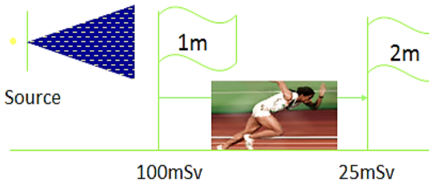


The following shielding guidelines can be used:

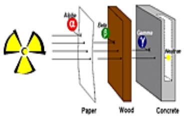
- Alpha particles (α) stopped by paper
- Beta particles (β) stopped by wood or Plexiglas
- **Gamma (γ) and X-rays (X) stopped by lead or concrete**
- Neutrons (η) absorbed by hydrogen-rich materials

MAINTAIN DISTANCE

- Distance
  - Greater the distance lesser is the dose
  - Dose decreases by inverse square law
- Tips
  - Do not put your arm in line with the primary beam
  - If the distance is doubled, the radiation dose becomes 25%
  - A recommended distance is 3 feet from the source.



USE EFFECTIVE SHIELDING



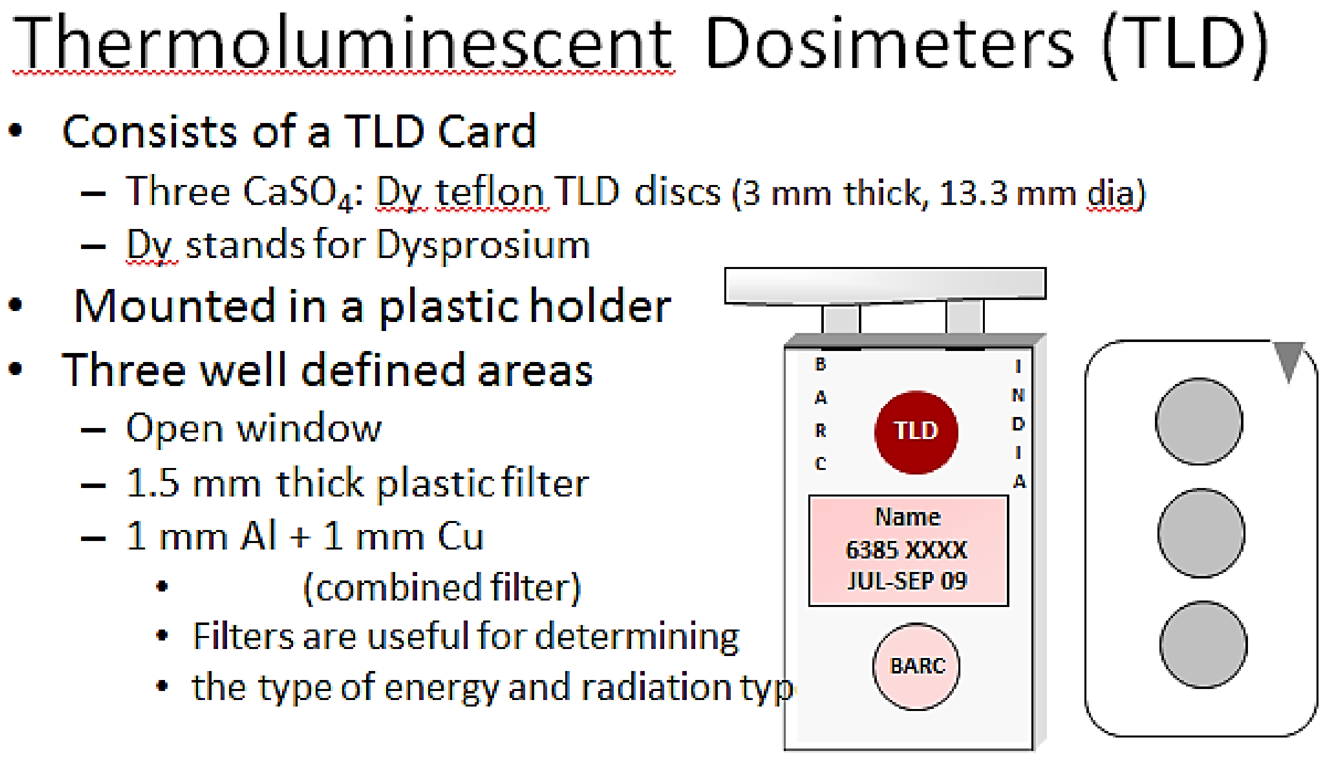
Placing radiation absorbing material between the source of radiation and people working nearby is considered as **SHIELDING**

LEAD APRON

- 0.25 mm lead equivalent thickness can stop 90% of the radiation
- ***0.5 mm lead equivalent thickness can stop almost 99% of the radiation***

Wear a lead apron

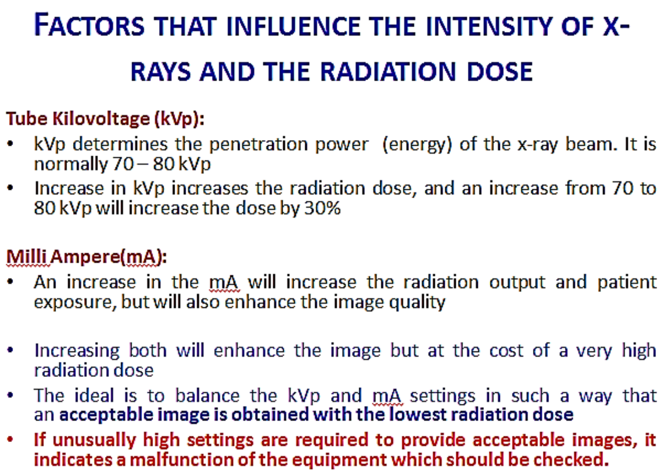
Work behind the lead barrier



Thermoluminescent Dosimeters (TLD)

- Consists of a TLD Card
  - Three $CaSO_4$: Dy teflon TLD discs (3 mm thick, 13.3 mm dia)
  - Dy stands for Dysprosium
- Mounted in a plastic holder
- Three well defined areas
  - Open window
  - 1.5 mm thick plastic filter
  - 1 mm Al + 1 mm Cu
    - (combined filter)
    - Filters are useful for determining
    - the type of energy and radiation typ

B A R C
I N D I A
TLD
Name
6385 XXXX
JUL-SEP 09
BARC



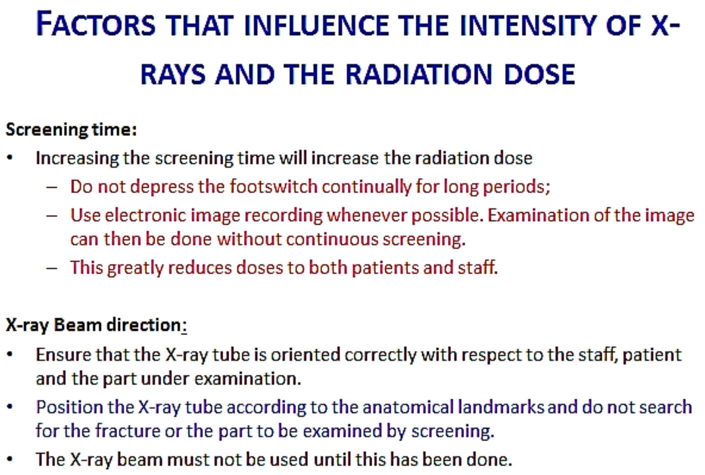
FACTORS THAT INFLUENCE THE INTENSITY OF X-RAYS AND THE RADIATION DOSE

Tube Kilovoltage (kVp):

- kVp determines the penetration power (energy) of the x-ray beam. It is normally 70 – 80 kVp
- Increase in kVp increases the radiation dose, and an increase from 70 to 80 kVp will increase the dose by 30%

Milli Ampere(mA):

- An increase in the mA will increase the radiation output and patient exposure, but will also enhance the image quality
- Increasing both will enhance the image but at the cost of a very high radiation dose
- The ideal is to balance the kVp and mA settings in such a way that an **acceptable image is obtained with the lowest radiation dose**
- **If unusually high settings are required to provide acceptable images, it indicates a malfunction of the equipment which should be checked.**



FACTORS THAT INFLUENCE THE INTENSITY OF X-RAYS AND THE RADIATION DOSE

Screening time:

- Increasing the screening time will increase the radiation dose
  - Do not depress the footswitch continually for long periods;
  - Use electronic image recording whenever possible. Examination of the image can then be done without continuous screening.
  - This greatly reduces doses to both patients and staff.

X-ray Beam direction:

- Ensure that the X-ray tube is oriented correctly with respect to the staff, patient and the part under examination.
- Position the X-ray tube according to the anatomical landmarks and do not search for the fracture or the part to be examined by screening.
- The X-ray beam must not be used until this has been done.

6. How to evaluate the function of a non-visualized kidney on IVU

A kidney may be non-visualized on IVU due to-

- renal agenesis
- post-nephrectomy
- poor function with or without obstruction
- in the presence of normal function during renal colic leading to renal artery spasm.

Non-contrast computerized tomography (CT) scan is an effective imaging tool for acute renal obstruction. With spiral scanners, images can be performed effectively without contrast media, take only 5 to 10 minutes to perform, and cost about the same as IVPs. In terms of benefits, the CT equals the accuracy of the IVP in determining the presence of obstruction, but surpasses the IVP in detecting the specific cause of the obstruction. Various signs of obstruction on spiral CT include hydroureter, perinephric stranding, hydronephrosis, periureteral oedema and renal swelling. However, a non-contrast CT does not indicate function of the kidneys.

MRI gives no added advantage over CT scan. In addition it does not visualise the stone. However, it correctly identifies the point of obstruction and the non-calculous causes of obstruction. MR excretory urography is a promising technique which affords equivalent functional and additional anatomical information to isotope renography. It is more accurate than Doppler ultrasound in the assessment of ureteric obstruction in pregnancy and is not associated with any risk of exposure to radiation, unlike IVU or renal scan.

Renal scan and diuretic renography is the most reliable technique to quantitatively assess the split and total renal function in the presence of hydronephrosis. It is a non-invasive study, can be done even in patients with deranged renal function, has no risk of contrast-induced nephrotoxicity and also has much less radiation exposure than IVP or CT scan. It can also be used to measure differential function and, therefore, is useful for treatment planning. Moreover, a functional obstruction can be differentiated from an anatomic cause. It can be used to follow up a patient after relief of obstruction. Also, the assessment of renal blood flow provides a sense of whether function may return upon relief of the obstruction. However, images from these scans lack the resolution to define the site of obstruction.

7. Bosniak classification-

Many cystic changes can occur in the kidney

From a radiological point of view, **cystic changes in the kidney** may be divided as follows:

(1) simple benign cortical renal cysts;

(2) simple benign parapelvic renal cysts;

(3) complex renal cysts;

(4) RCC with cystic changes;

(5) von Hippel–Lindau disease;

(6) renal cystadenoma (Perlman tumour);

(7) autosomal dominant polycystic kidney disease (ADPKD 1);

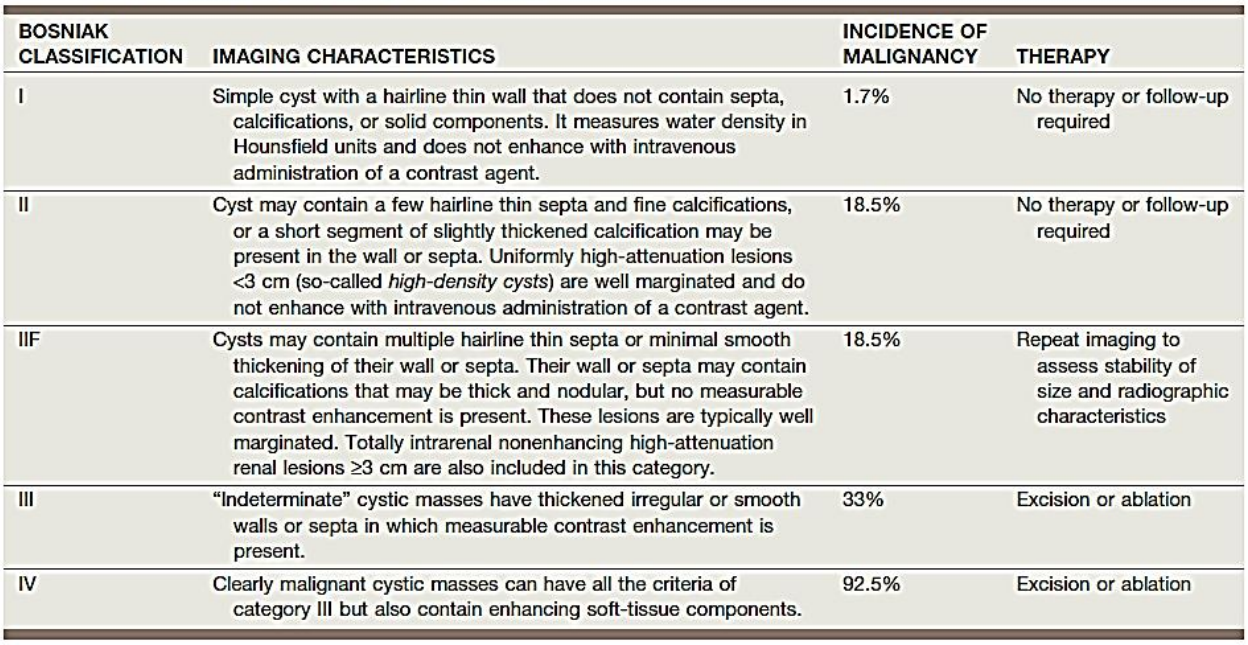
(8) autosomal recessive polycystic kidney disease (ADPKD);

(9) congenital nephrotic syndrome;

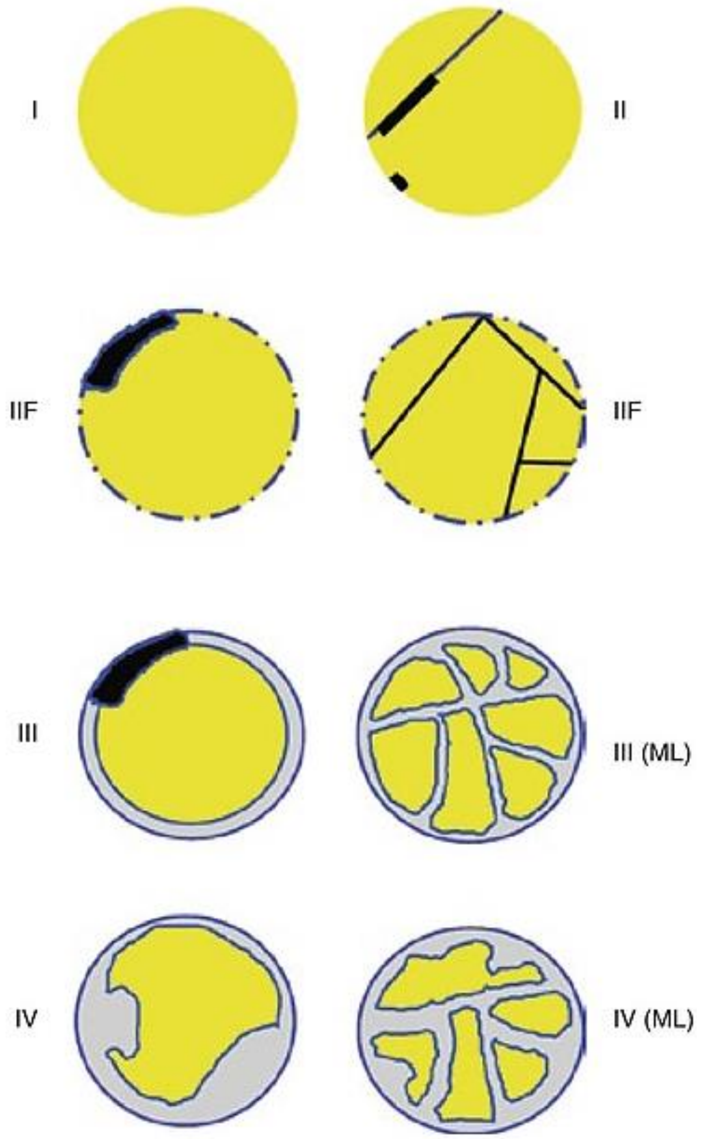
(10) cysts as a result of prolonged haemodialysis

(11) echinococcus cysts and other infectious cysts.

TABLE 56-1 Bosniak Classification of Renal Cysts

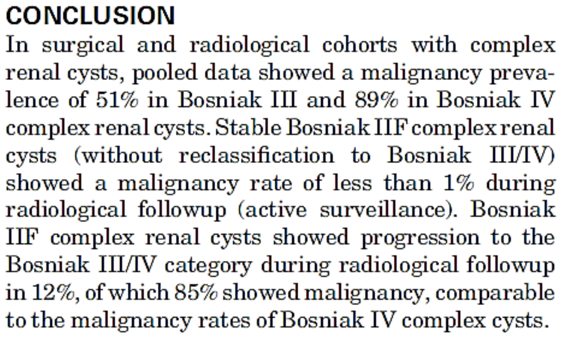


BOSNIAK CLASSIFICATION	IMAGING CHARACTERISTICS	INCIDENCE OF MALIGNANCY	THERAPY
I	Simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density in Hounsfield units and does not enhance with intravenous administration of a contrast agent.	1.7%	No therapy or follow-up required
II	Cyst may contain a few hairline thin septa and fine calcifications, or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high-attenuation lesions <3 cm (so-called *high-density cysts*) are well marginated and do not enhance with intravenous administration of a contrast agent.	18.5%	No therapy or follow-up required
IIF	Cysts may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Their wall or septa may contain calcifications that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are typically well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions ≥3 cm are also included in this category.	18.5%	Repeat imaging to assess stability of size and radiographic characteristics
III	"Indeterminate" cystic masses have thickened irregular or smooth walls or septa in which measurable contrast enhancement is present.	33%	Excision or ablation
IV	Clearly malignant cystic masses can have all the criteria of category III but also contain enhancing soft-tissue components.	92.5%	Excision or ablation



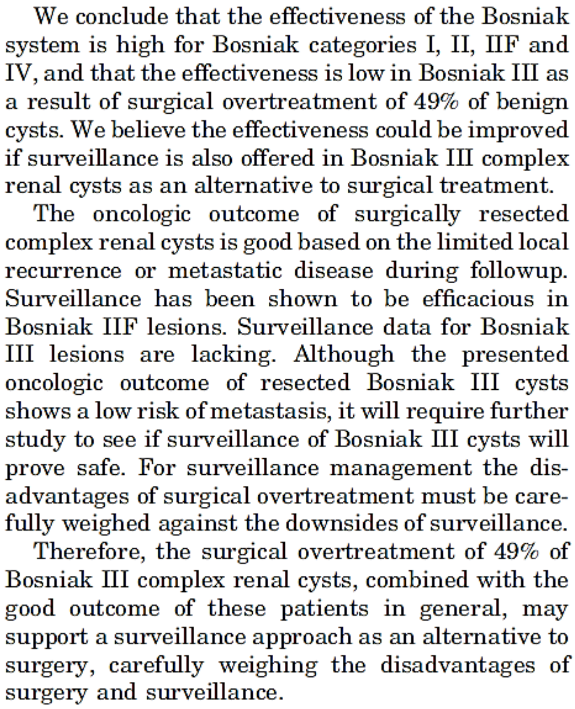
Drawing of the different categories of renal cystic masses according to Bosniak classification. *ML* multilocular

Recent Review has shown-



CONCLUSION

In surgical and radiological cohorts with complex renal cysts, pooled data showed a malignancy prevalence of 51% in Bosniak III and 89% in Bosniak IV complex renal cysts. Stable Bosniak IIF complex renal cysts (without reclassification to Bosniak III/IV) showed a malignancy rate of less than 1% during radiological followup (active surveillance). Bosniak IIF complex renal cysts showed progression to the Bosniak III/IV category during radiological followup in 12%, of which 85% showed malignancy, comparable to the malignancy rates of Bosniak IV complex cysts.



We conclude that the effectiveness of the Bosniak system is high for Bosniak categories I, II, IIF and IV, and that the effectiveness is low in Bosniak III as a result of surgical overtreatment of 49% of benign cysts. We believe the effectiveness could be improved if surveillance is also offered in Bosniak III complex renal cysts as an alternative to surgical treatment.

The oncologic outcome of surgically resected complex renal cysts is good based on the limited local recurrence or metastatic disease during followup. Surveillance has been shown to be efficacious in Bosniak IIF lesions. Surveillance data for Bosniak III lesions are lacking. Although the presented oncologic outcome of resected Bosniak III cysts shows a low risk of metastasis, it will require further study to see if surveillance of Bosniak III cysts will prove safe. For surveillance management the disadvantages of surgical overtreatment must be carefully weighed against the downsides of surveillance.

Therefore, the surgical overtreatment of 49% of Bosniak III complex renal cysts, combined with the good outcome of these patients in general, may support a surveillance approach as an alternative to surgery, carefully weighing the disadvantages of surgery and surveillance.

8. Role of 3D reconstruction in CT-

Production of a 3D image involves a stepwise sequence of data acquisition, interpolation, rendering and visualization . First and foremost, data must be acquired as a complete volume, i.e. its orientation in the three spatial planes (x, y, z) needs to be registered. For CT and MRI this is not difficult,as the relationship of the scanner table to the scanning plane is always known (the z axis).

CLINICAL APPLICATIONS OF 3D CT-

1. **CT/MR LOWER TRACT ENDOSCOPY**
   Because it has a simple morphology, ease of access and lack of peristalsis, the bladder was the first urinary tract organ to be assessed by virtual endoscopy. The bladder can be visualized using air, CO 2 or intravenous contrast media . Most earlier CT studies used thick CT slices for reconstruction, with perspective surface rendering, and therefore produced poor results that were not good at discriminating sessile/flat lesions or lesions of < 5 mm . Also, the insufflation technique was invasive and this drawback

eliminated the potential advantage of virtual over conventional cystoscopy. Improved results have subsequently been obtained using intravenous contrast agent, multidetector row CT (MDCT) and volume rendering .

2. **CT/MR UPPER TRACT ENDOSCOPY**
   Virtual endoscopic studies of the upper tract to date are limited. CT nephroscopy detected 92% of renal pelvis urothelial tumours, vs 83% for axial CT, when compared to histopathological specimens. CT ureteroscopy has a sensitivity of 81% and specificity of 100% for ureteric tumours. Again, as with virtual cystoscopy, sessile lesions were more difficult to detect than pedunculated lesions. Examination with MDCT and perspective volume rendering may produce better results.

3. **SURGICAL PLANNING**

- **RENAL SURGERY**
  3D CT rendered images on a workstation provide an interactive display combining axial CT, excretory urography and angiography. Volume-rendered 3D CT reconstruction of renal tumours before NSS is now routine and detected all lesions accurately, along with 96% of renal arteries and 93% of renal veins. Pre-nephrectomy 3D CT detected 93% of renal lesions with 97% detection for renal arteries and 100% for renal veins. The kidney, tumour position and landmarks were clearly defined.

- **PUJ OBSTRUCTION**
  CT rendering can provide comprehensive images before endourological procedures to treat PUJ obstruction, including establishing the presence and relationship of crossing vessels to the renal pelvis . Although CT angiography is better than 3D CT in depicting crossing vessel position, surface-rendered images display the spatial relationship of the vessel to the pelvis, and have been shown to subjectively and positively influence surgical planning . CT endoscopy has also been used after treating PUJ obstruction by metallic stenting, using virtual navigation to assess stent patency

- **STONE SURGERY**
  Recent work has concentrated on 3D reconstruction of the actual calculus. In a series of patients using non-contrast 3D CT, they used surface-rendered images to show the complex morphology of large renal calculi. 3D reconstructionsubjectively facilitated endoscopic exploration and removal of calculi. In a third of patients the authors altered the access site that would have been adopted if the corresponding axial CT and IVU images had been used. Experimental studies on pig kidneys using 3D CT volume rendering assisted by virtual renoscopy have been promising. The combination of the diagnostic accuracy of CT with 3D modelling for appreciating the location of calculus and calyceal anatomy may displace the IVU completely.

CONCLUSION

The inherent attraction of 3D imaging for surgeons is the appreciation of spatial relationships in a way that conventional images are unable to portray. However, it is not necessary for 3D modelling to be applied to every investigation unless extra information is to be gained. Factors such as patient acceptability, tolerance, safety, convenience and cost must always be considered.

10. PET in Urological cancers (essay)

- The most recent advance in nuclear scintigraphy is in the detection of primary and metastatic cancer using Positron emission tomography (PET).
- Radiotracers have been developed to be incorporated in to dividing cells or cellular mechanisms involved in the increased metabolic activity of malignancies, which can then be detected using PET imaging.

- Combining PET with high-resolution CT (PET/ CT) has the ability to increase our detection of recurrent or metastatic urologic cancers.

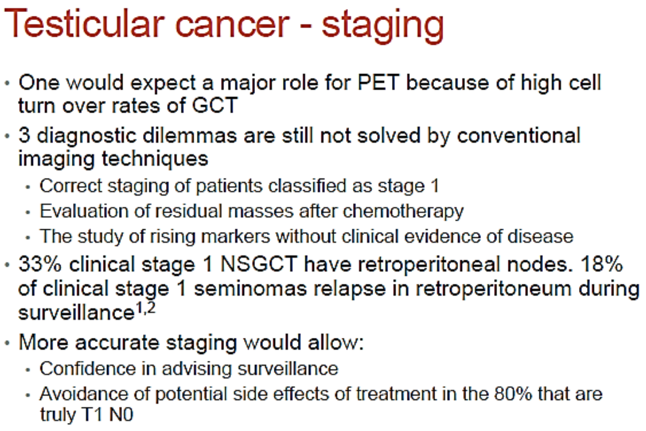
RADIO ISOTOPES IN PET

18F fluorodeoxyglucose (FDG)

- First introduced in 1976.
- This isotope takes advantage of *increased glycolysis and decreased dephosphorylation* in some malignant cells.
- Transported in to cancer cells, where it is preferentially retained relative to normal tissue as there is arrest in the metabolism of glucose in malignant cells
- This allows detection of some primary and metastatic cancers using PET/CT imaging.

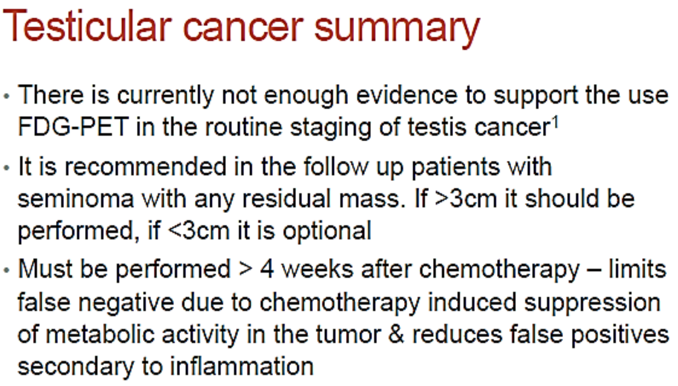
UROLOGICAL APPLICATIONS :

Testis cancer



Testicular cancer - staging

- One would expect a major role for PET because of high cell turn over rates of GCT
- 3 diagnostic dilemmas are still not solved by conventional imaging techniques
  - Correct staging of patients classified as stage 1
  - Evaluation of residual masses after chemotherapy
  - The study of rising markers without clinical evidence of disease
- 33% clinical stage 1 NSGCT have retroperitoneal nodes. 18% of clinical stage 1 seminomas relapse in retroperitoneum during surveillance[1,2]
- More accurate staging would allow:
  - Confidence in advising surveillance
  - Avoidance of potential side effects of treatment in the 80% that are truly T1 N0



Testicular cancer summary

- There is currently not enough evidence to support the use FDG-PET in the routine staging of testis cancer[1]
- It is recommended in the follow up patients with seminoma with any residual mass. If >3cm it should be performed, if <3cm it is optional
- Must be performed > 4 weeks after chemotherapy – limits false negative due to chemotherapy induced suppression of metabolic activity in the tumor & reduces false positives secondary to inflammation

- PET had a higher sensitivity (70% vs 40%) and a higher specificity (100% vs 78%) when compared to CT in detecting retroperitoneal lymphnodes
- Limitations of PET
  - ➢ Inability to detect metastatic lesions *less than 5 mm in diameter.*
  - ➢ *Low sensitivity for detecting mature teratoma,* which has a low glucose metabolic rate.
- Useful in post chemotherapy evaluation of a residual mass in the retroperitoneum.
- The differentiation between residual tumor, fibrosis, and teratoma can play a significant role in guiding further therapy.
- PET / CT was found to have a higher diagnostic accuracy than CT for staging and restaging in the assessment of a CT-visualized *residual mass following chemotherapy* for seminoma and non seminomatous germ cell tumors
- Overall the *sensitivity and specificity was 89% and 100%, respectively*.
- The accuracy of PET seems to be compromised if performed within 2 weeks of completion of chemotherapy, likely due to decreased metabolism and increased macrophage activity
- Recommended that PET/CT be *delayed for 4 to 12 weeks following completion of chemotherapy.*
- Beneficial in monitoring the response of retroperitoneal disease to therapy, with a decrease in FDG uptake correlating with a positive response to treatment.

Renal cell carcinoma

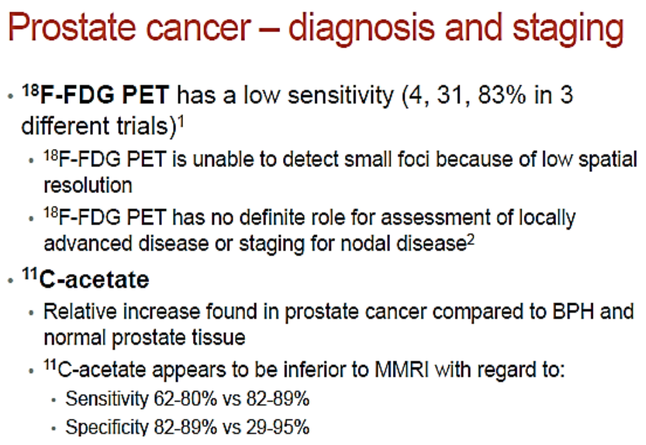
- PET appears to be more accurate in monitoring for progression of disease, metastasis, or local recurrence in the renal fossa bed.
- Demonstrated to be invaluable in monitoring progression of treated RCC in the form of local recurrence or metastasis.

- *100% accuracy in demonstrating local recurrence and metastases as opposed to 88% for CT.*
- Able to better *differentiate between a recurrent mass in the renal fossa bed and radiation necrosis* when compared to CT.
- *Useful in characterizing indeterminate lesions* identified on conventional imaging in patients with a history of metastatic RCC.
- Lymph node staging with CT has been found to have a sensitivity of 83% to 89%, imaging with PET has demonstrated an increased sensitivity of 100%
- Useful in demonstrating an RCC metastasis to the *intramedullary spinal cord.*
- Have superiority over bone scan in detecting active osseous metastasis of RCC.

In Clear cell renal carcinoma

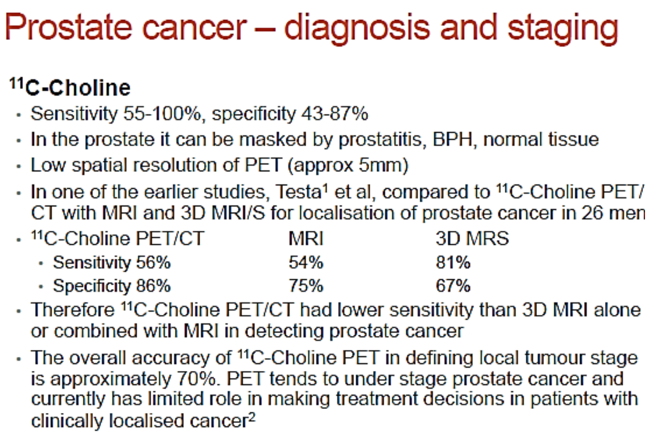
- An *antibody (cG250) recognizing carbonic anhydrase IX* has been developed. Carbonic anhydrase IX is a protein related to the unrestrained growth of clear cell renal cancers.
- A positron emitting *radionuclide (iodine 124)* has been attached to the cG250 Antibody and injected into renal cell cancer patients.
- The radionuclide - antibody complex attaches to the carbonic anhydrase IX protein from clear cell renal cancer cells and can be detected on PET/CT imaging.
- *94% sensitivity and 100% specificity in renal cell carcinoma*

Prostate cancer.



Prostate cancer – diagnosis and staging

- **^{18}F-FDG PET** has a low sensitivity (4, 31, 83% in 3 different trials)[1]
  - ^{18}F-FDG PET is unable to detect small foci because of low spatial resolution
  - ^{18}F-FDG PET has no definite role for assessment of locally advanced disease or staging for nodal disease[2]
- **^{11}C-acetate**
  - Relative increase found in prostate cancer compared to BPH and normal prostate tissue
  - ^{11}C-acetate appears to be inferior to MMRI with regard to:
    - Sensitivity 62-80% vs 82-89%
    - Specificity 82-89% vs 29-95%



Prostate cancer – diagnosis and staging

^{11}C-Choline

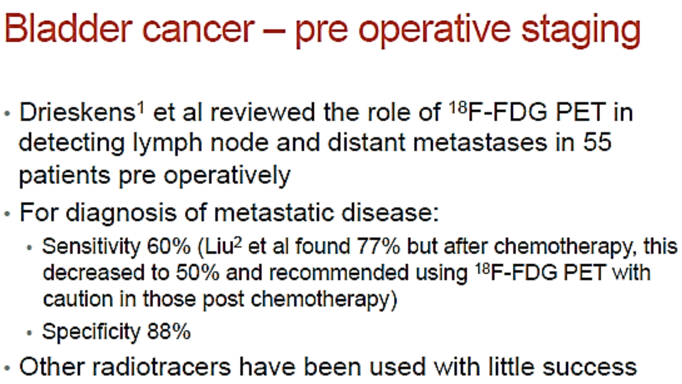
- Sensitivity 55-100%, specificity 43-87%
- In the prostate it can be masked by prostatitis, BPH, normal tissue
- Low spatial resolution of PET (approx 5mm)
- In one of the earlier studies, Testa[1] et al, compared to ^{11}C-Choline PET/CT with MRI and 3D MRI/S for localisation of prostate cancer in 26 men

^{11}C-Choline PET/CT	MRI	3D MRS
Sensitivity 56%	54%	81%
Specificity 86%	75%	67%

- Therefore ^{11}C-Choline PET/CT had lower sensitivity than 3D MRI alone or combined with MRI in detecting prostate cancer
- The overall accuracy of ^{11}C-Choline PET in defining local tumour stage is approximately 70%. PET tends to under stage prostate cancer and currently has limited role in making treatment decisions in patients with clinically localised cancer[2]

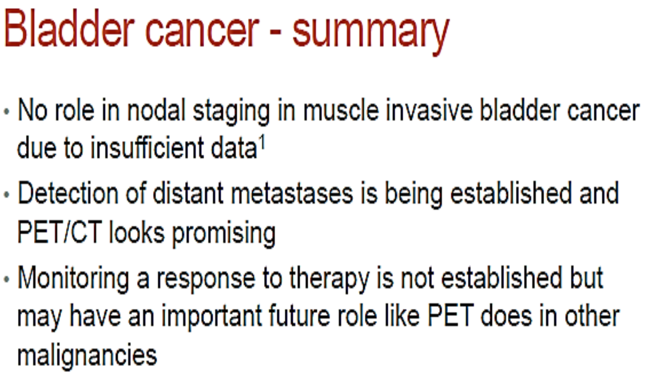
- At least seven tracers are being investigated. Each tracer is directed at a different part of cell function such as *glycolysis, amino acid transport, choline kinase activity, fatty acid synthesis, androgen receptor, and bone mineralization.*
- Use of FDG-PET is disappointing - *most prostate cancers have a relatively low glycolytic rate* and therefore do not accumulate high concentrations of the radiotracer FDG.
- *11C-choline, an alternative radiotracer* with negligible urinary excretion that is taken up in cancer cells by active transport and retained by phosphorylation.
- Cervical spinal metastases are more easily detected by PET than by bone scintigraphy.
- *PET could detect twice as many bony metastases (anywhere) compared to bone scintigraphy.*
- Most promising indication for PET -- *Ability to evaluate changes in tumor burden and location of disease during therapy* and, thus, to determine the prognosis of the patient.
- Studies have demonstrated that changes in PET scanning correlate with changes in PSA.
- PET can potentially be employed to both quantify and localize the effects of treatment of metastatic prostate cancer and help guide further therapy.
- FDG-PET was able to detect local or systemic recurrence in only 34% of patients.

Bladder cancer



Bladder cancer – pre operative staging

- Drieskens[1] et al reviewed the role of ^{18}F-FDG PET in detecting lymph node and distant metastases in 55 patients pre operatively
- For diagnosis of metastatic disease:
  - Sensitivity 60% (Liu[2] et al found 77% but after chemotherapy, this decreased to 50% and recommended using ^{18}F-FDG PET with caution in those post chemotherapy)
  - Specificity 88%
- Other radiotracers have been used with little success



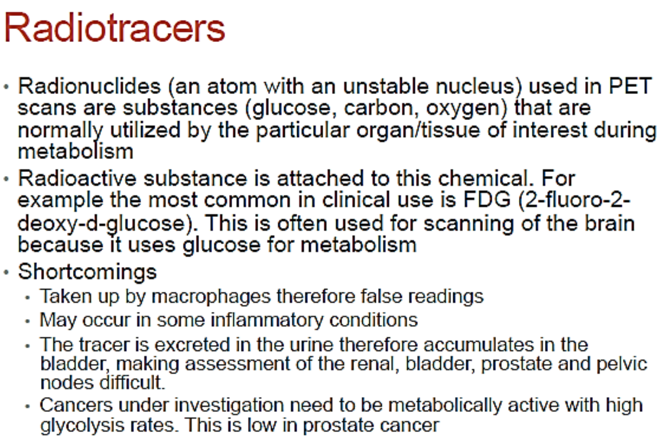
Bladder cancer - summary

- No role in nodal staging in muscle invasive bladder cancer due to insufficient data[1]
- Detection of distant metastases is being established and PET/CT looks promising
- Monitoring a response to therapy is not established but may have an important future role like PET does in other malignancies

- FDG is renal excreted and not useful in bladder cancer.
- Accumulation of the excreted tracer in the bladder despite bladder irrigation and Foley drainage
- Only 78% of bladder cancer could be visualized using 11C-methioninie tracer, and PET did not improve local staging of the disease.
- 11 C-choline was also found to be a poor predictor of primary or metastatic urothelial carcinoma.
- It may help identify lymph node and distant metastases and may help in differentiating recurrent disease from tissue changes following radiation.

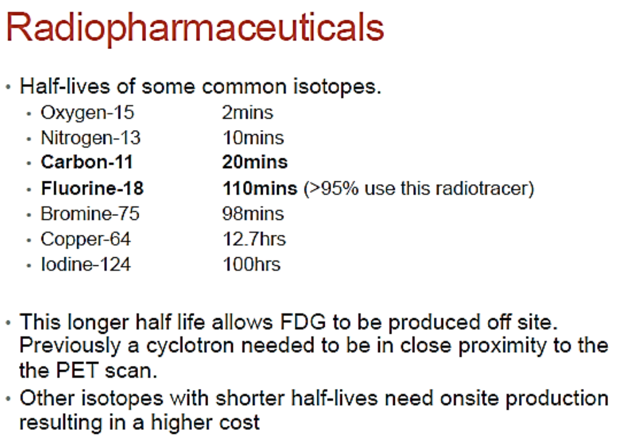
PET/CT in urologic oncology is in its infancy.
PET has the capability of demonstrating in vivo gene expression.
As a result, the ultimate utility may transcend diagnostic imaging and allow determination of the efficacy of targeted gene therapy.

EXTRA-



Radiotracers

- Radionuclides (an atom with an unstable nucleus) used in PET scans are substances (glucose, carbon, oxygen) that are normally utilized by the particular organ/tissue of interest during metabolism
- Radioactive substance is attached to this chemical. For example the most common in clinical use is FDG (2-fluoro-2-deoxy-d-glucose). This is often used for scanning of the brain because it uses glucose for metabolism
- Shortcomings
  - Taken up by macrophages therefore false readings
  - May occur in some inflammatory conditions
  - The tracer is excreted in the urine therefore accumulates in the bladder, making assessment of the renal, bladder, prostate and pelvic nodes difficult.
  - Cancers under investigation need to be metabolically active with high glycolysis rates. This is low in prostate cancer

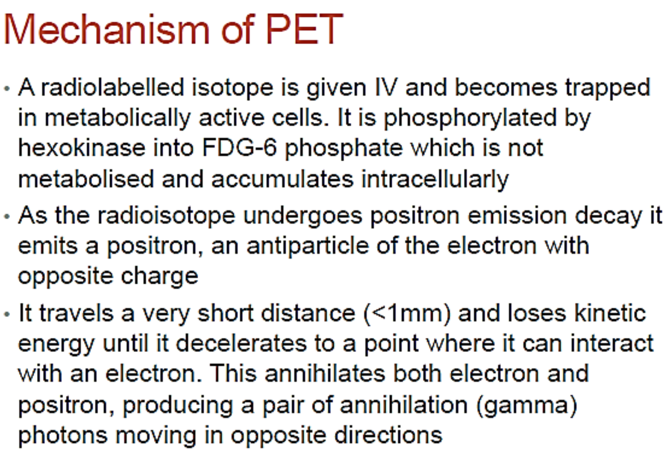


Radiopharmaceuticals

- Half-lives of some common isotopes.

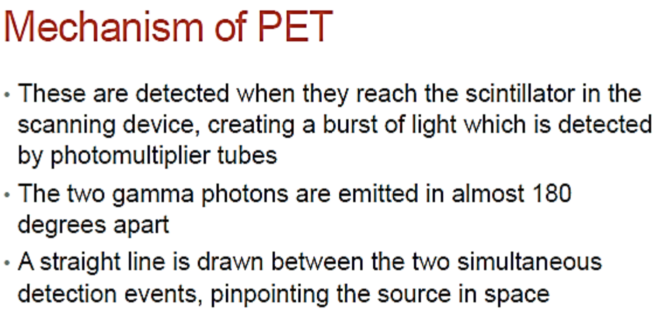
Oxygen-15	2mins
Nitrogen-13	10mins
Carbon-11	**20mins**
Fluorine-18	**110mins** (>95% use this radiotracer)
Bromine-75	98mins
Copper-64	12.7hrs
Iodine-124	100hrs

- This longer half life allows FDG to be produced off site. Previously a cyclotron needed to be in close proximity to the the PET scan.
- Other isotopes with shorter half-lives need onsite production resulting in a higher cost



Mechanism of PET

- A radiolabelled isotope is given IV and becomes trapped in metabolically active cells. It is phosphorylated by hexokinase into FDG-6 phosphate which is not metabolised and accumulates intracellularly
- As the radioisotope undergoes positron emission decay it emits a positron, an antiparticle of the electron with opposite charge
- It travels a very short distance (<1mm) and loses kinetic energy until it decelerates to a point where it can interact with an electron. This annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in opposite directions



Mechanism of PET

- These are detected when they reach the scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes
- The two gamma photons are emitted in almost 180 degrees apart
- A straight line is drawn between the two simultaneous detection events, pinpointing the source in space

9. dwMRIin Urological cancers-Pl read attached E Urol review

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European Association of Urology

Review – Imaging

Potential and Limitations of Diffusion-Weighted Magnetic Resonance Imaging in Kidney, Prostate, and Bladder Cancer Including Pelvic Lymph Node Staging: A Critical Analysis of the Literature

Gianluca Giannarini[a], *Giuseppe Petralia*[b], *Harriet C. Thoeny*[b,*]

[a] *Department of Urology, University Hospital of Bern, Inselspital, Bern, Switzerland;* [b] *Institute of Diagnostic, Interventional, and Paediatric Radiology, University Hospital of Bern, Inselspital, Bern, Switzerland*

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Abstract

Context: Diagnosis, staging, and treatment monitoring are still suboptimal for most genitourinary tumours. Diffusion-weighted magnetic resonance imaging (DW-MRI) has already shown promise as a noninvasive imaging modality in the early detection of microstructural and functional changes in several pathologies of various organs.

Objective: To assess the potential and limitations of DW-MRI in the management of patients with kidney, prostate, and bladder cancer.

Evidence acquisition: A nonsystematic literature search using the Medline/PubMed and Embase databases for full-length papers reporting on DW-MRI for kidney, prostate, and bladder cancer was performed up to August 1, 2011. Only those articles with complete data reporting on DW-MRI applications with potential implications in solving commonly encountered clinical challenges relating to tumour detection, staging, and treatment monitoring were finally examined.

Evidence synthesis: For kidney tumours DW-MRI is a reasonable alternative to conventional cross-sectional imaging to detect and characterise focal renal lesions, especially in patients with impaired renal function. For prostate cancer, DW-MRI applied in addition to conventional T2-weighted and contrast-enhanced magnetic resonance imaging (MRI) improves tumour detection and localisation. In addition, it has shown promise for the assessment of tumour aggressiveness and for treatment monitoring during active surveillance, radiation therapy, and focal therapy. For bladder cancer, DW-MRI may improve the performance of conventional T2-weighted and contrast-enhanced MRI in the work-up of bladder cancer, helping to differentiate non–muscle-invasive from muscle-invasive tumours. For pelvic lymph nodes, initial results showed the potential to improve nodal staging of prostate and bladder cancer compared with conventional cross-sectional imaging.

Conclusions: DW-MRI holds promise to ameliorate the management of patients with kidney, prostate, and bladder cancer including pelvic lymph node staging. Current limitations include the lack of standardisation of the technique across multiple centres and the still limited expertise.

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* Corresponding author. Institute of Diagnostic, Interventional, and Paediatric Radiology, University Hospital of Bern, Inselspital, CH-3010 Bern, Switzerland. Tel. +41 31 632 2939; Fax: +41 31 632 4874.
E-mail address: harriet.thoeny@insel.ch (H.C. Thoeny).

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1. Introduction

Contrast-enhanced (CE) computed tomography (CT) and conventional magnetic resonance imaging (MRI) are established imaging techniques for the work-up of genitourinary tumours. Kidney tumours are routinely diagnosed and staged with CE-CT or in selected cases with MRI. Locoregional staging of prostate cancer (PCa) and bladder cancer (BCa) is usually performed with MRI, whereas CE-CT is used to search for metastases. However, the characterisation of focal renal lesions, especially in patients with impaired renal function, and the detection and staging of PCa and BCa as well as pelvic lymph node (LN) staging are issues that often remain unresolved using conventional cross-sectional imaging.

Diffusion-weighted MRI (DW-MRI) is a noninvasive technique measuring the microscopic mobility of water molecules in the tissues without contrast administration. This mobility depends on the integrity of cell membranes and the cellularity of the underlying tissue, thus reflecting biologic abnormalities [1]. DW-MRI was first applied in the brain, where it became the gold standard for the diagnosis of acute stroke because microstructural changes observed on DW-MRI precede morphologic changes detected on conventional cross-sectional imaging [2,3]. Extracranial applications are more challenging, however, because of physiologic motion artefacts (ie, respiration, cardiac, and bowel motion) [4]. Owing to continuous technical improvements including fast sequences, DW-MRI has been increasingly applied in the abdomen and pelvis for functional applications, tumour detection and characterisation, as well as monitoring of treatment response in various organs [4,5].

This review provides a critical overview of the current literature on DW-MRI for the work-up of kidney tumours, PCa, and BCa, as well as for pelvic LNs, emphasising its potential and limitations in everyday clinical practice.

2. Evidence acquisition

A nonsystematic literature search using the Medline/PubMed and Embase databases for full-length papers and including both medical subject headings and free-text protocols was performed up to August 1, 2011. Entry terms were *diffusion-weighted magnetic resonance imaging* in conjunction with *kidney* OR *renal*, *prostat** and *bladder tumour* OR *cancer* OR *carcinoma* OR *neoplasm**, and *pelvic lymph nodes*. Search limitations were title/abstract, humans, all adults, and English language.

Two authors (GG and GP) reviewed the abstracts of the retrieved records and selected only those pertinent to the objectives of the present analysis. Contrasts were eventually solved by the senior author (HCT). All authors then carefully analysed the corresponding full-length articles, and additional referenced papers of interest were identified by hand search and retrieved.

Review articles, case reports, and congress abstracts were excluded. Feasibility studies, papers focusing on technical aspects of DW-MRI, as well as papers published before 2006 were preferentially excluded. Only those articles with complete data reporting on DW-MRI applications with potential implications to solve common challenges encountered in the routine clinical scenario, namely dilemmas in tumour detection, staging, and treatment monitoring for the three most frequent genitourinary tumours including pelvic LN staging of PCa and BCa, were finally analysed.

3. Evidence synthesis

The combined search generated a total of 259 papers. From the retrieved material, 71 papers, 13 for kidney tumours, 44 for PCa, 10 for BCa, and 4 for pelvic LN staging, were selected for final analysis. No study was specifically designed based on the Standards for Reporting of Diagnostic Accuracy guidelines [6], which are the recommended methodology for reporting studies of diagnostic accuracy.

3.1. *Basic principles and technical requirements of diffusion-weighted magnetic resonance imaging*

DW-MRI is an MRI technique that visualises molecular diffusion, that is, the Brownian motion of water molecules in biologic tissues [1], by applying two equally size but opposite diffusion-sensitising gradients, which are characterised by their b-values. The mobility is then quantified by calculating the apparent diffusion coefficient (ADC), which depends mainly on the choice of the underlying b-values. The lower the b-value applied, the higher the resulting ADC value. Image interpretation can be performed qualitatively by visual assessment of the DW images and the corresponding ADC map, and quantitatively by measuring the ADC value of the lesion. This ADC combines the effects of capillary perfusion and water diffusion in the extracellular extravascular space, providing simultaneous information on perfusion and diffusion in any organ [1]. Thus DW-MRI can be used to better differentiate normal and abnormal tissues at an early point in time, and it may improve detection and characterisation of various abnormalities preceding morphologic changes on conventional MRI. When comparing ADC values in the literature for any organ and lesion, attention has to be paid to the choice of the underlying b-values [7].

Hypercellular tumours lead to impeded movement in the interstitial space and are therefore depicted as hyperintense (bright) lesions on the high b-value images (eg, b = 1000s/mm^2) and hypointense (dark) lesions on the corresponding ADC map (low measured ADC value). A cystic or necrotic lesion, however, contains few restrictions to movement and is therefore dark on the high b-value images and bright on the ADC map, with resulting ADC values higher than those of a solid lesion.

Currently, nearly all available clinical systems (1.5 T and 3 T) have the capability of performing DW-MRI examinations in addition to morphologic/anatomic imaging. For genitourinary tumours, most DW acquisitions are performed in the axial plane either in “free breathing” or with “respiratory triggering” in addition to the conventional MRI sequences, with an extra time of approximately 4 min for the former and 10 min for the latter. This allows comprehensive information on morphologic and functional information during one examination without contrast medium administration. The administration of an antiperistaltic agent such as glucagon or hyoscine-N-butyl bromide can further improve image quality by reducing bowel motion artefacts. However, susceptibility artefacts from hip prostheses usually impair the quality of DW-MRI sequences, thus limiting its application in these patients.

No studies are available so far comparing the diagnostic performance of DW-MRI for prostate and bladder using endorectal versus phased-array body coils. There is some controversy among researchers whether the endorectal coil should be used for prostate imaging. The endorectal coil is recommended when performing MRI at 1.5 T by several radiologists; however, excellent image quality mainly at 3 T, but also at 1.5 T, can be achieved even with phased-array coils, resulting in improved patient comfort and reduced cost. Conversely, there is agreement about the lack of benefit in using the endorectal coil for bladder imaging. Technical details concerning DW-MRI, image parameters, and acquisition techniques can be found in previously published reviews [4,8].

3.2. *Kidney tumours*

3.2.1. *Detection and characterisation*

Although conventional cross-sectional imaging identifies a malignant renal lesion with high accuracy, in specific cases the differentiation between complicated cyst and cystic renal cell carcinoma (RCC), as well as between benign and malignant solid lesions (ie, oncocytoma and RCC) or among different malignant cell types remains difficult or even impossible. In these cases, DW-MRI might be useful thanks to different ADC values observed in benign and malignant lesions as well as in tumour subtypes due to their different cellularity.

The ability of ADC values to characterise focal renal lesions (viable solid tumours, necrotic or cystic tumour areas and cysts) was explored in a study including 25 patients with 26 renal tumours and 11 benign cysts on definitive histology [9]. Renal tumours had significantly lower median ADC values compared with benign cysts, and solid enhancing tumours had significantly lower ADC values compared with necrotic or cystic regions, which in turn had lower ADC values compared with benign cysts. This was likely due to nonviable tissue in necrotic tumours that did not enhance but resulted in impeded diffusion as compared with cystic fluid. There was, however, an overlap of ADC values across the different categories. When renal lesions were stratified by T1 signal characteristics, T1 hyperintense lesions had lower ADC values compared with their hypointense counterparts, and overlap decreased. In another study of 41 patients with 64 non–fat-containing T1 hyperintense renal lesions [10], mean ADC values for RCC were significantly lower than those for haemorrhagic or proteinaceous cysts. In a further study of 42 patients with 69 focal renal lesions, the ADC values of 7 cystic RCCs were significantly lower ($p < 0.001$) than those of 31 simple cysts [11]. Another study [12] failed to confirm these findings because no difference between benign cysts and cystic areas of RCC was observed. In that study, ADC values for renal oncocytoma were significantly higher ($p = 0.0097$) than those for solid RCC. All these studies, however, included only a limited number of patients, and the reported ADC values showed a non-negligible overlap, although the difference in ADC values between benign and malignant renal lesions was statistically significant. Therefore, the ability of ADC values to discriminate benign from malignant cystic lesions is still limited in the everyday clinical setting where decisions have to be made on the individual patient.

DW-MRI has also been investigated in an attempt to differentiate the various RCC subtypes, which is critical for both prognostication and the selection of appropriate systemic therapies for patients with metastatic disease [13]. Contrasting results have been reported in the literature. In a study including 83 patients with 85 tumours [14], at b-values of 0 and 800 s/mm^2, mean ADC values for 49 clear cell RCCs were significantly higher ($p < 0.001$) than those for 22 papillary RCCs and 14 chromophobic RCCs, whereas in a study of 32 patients [15], at b-values of 0, 300, and 1000s/mm^2, significantly lower ADC values ($p = 0.0004$) were reported for clear cell RCC than for non–clear cell RCC. No significant difference between mean ADC values of clear cell RCCs and those of non–clear cell RCCs was found in another study including 17 malignant lesions [11]. A possible explanation for this discrepancy could be related to differences in image analysis (eg, delineation of region of interest including necrotic areas leading to higher ADC values) and limited sample size for subgroup analysis. Table 1 specifies the details of recently published studies on kidney tumours [9–12,14–22].

A commonly encountered challenge is the characterisation of focal renal lesions in patients with impaired renal function. In these cases, contrast medium administration should be avoided because of the risk of contrast-induced nephropathy with CT or nephrogenic systemic fibrosis with MRI. DW-MRI could thus be extremely useful in this setting. In the previously mentioned study including 109 focal renal lesions (81 benign lesions and 28 RCCs) [12], the diagnostic performance of DW-MRI was compared with that of CE-MRI. Sensitivity and specificity for the diagnosis of malignancy were only slightly lower for DW-MRI (86% and 80%, respectively) than for CE-MRI (100% and 89%, respectively). In the other previously mentioned study including 64 complex cystic masses [10], the diagnostic performance of DW-MRI (71% sensitivity and 91% specificity) was similar to that of the contrast enhancement ratio (65% sensitivity and 96% specificity) in predicting malignancy. Therefore, it may be concluded that DW-MRI is a reasonable alternative to CE-MRI for the characterisation of focal renal lesions in patients with impaired renal function (Fig. 1).

3.2.2. *Local staging/treatment monitoring*

No publications on the use of DW-MRI in locoregional staging or the prediction and monitoring of treatment response for kidney tumours could be found.

Table 1 – Recently published studies reporting apparent diffusion coefficient values for kidney tumours of different histology

Study	No. of patients	No. of tumours	Imaging		ADC value ($\times 10^{-3}$ mm^2/s) (mean ± standard deviation)									Reference standard	Sensitivity, %	Specificity, %	Threshold ADC value, $\times 10^{-3}$ mm^2/s
			Field strength, T	b-values, s/mm^2	Papillary RCC	Clear cell RCC	Chromophobic RCC	Nonpapillary RCC	Non–clear cell RCC	Oncocytoma	Solid RCC	Cystic RCC	Benign cysts				
Yoshikawa et al. [16]	NR	87	1.5	0, 600	–	–	–	–	–	–	2.49 ± 0.72	–	3.82 ± 0.39	H, I, and FU	NR	NR	–
Zhang et al. [9]	25	26	1.5	0, 500, 1000	–	–	–	–	–	–	1.72 ± 0.47	2.22 ± 0.64	3.27 ± 0.62	H	NR	NR	–
Manenti et al. [17]	27	27	3	0, 500	1.81 ± 0.4	1.74 ± 0.6	1.74 ± 0.7	–	–	–	–	–	–	H	NR	NR	–
Kim et al. [10]	41	64	1.5	0, 400	–	–	–	–	–	–	1.75 ± 0.57	–	2.50 ± 0.53 (haemorrhagic)	H and FU	71	91	1.88
Taouli et al. [12]	64	109	1.5	0, 400, 800	1.12 ± 0.18	–	–	1.62 ± 0.73	–	1.91 ± 0.97	1.54 ± 0.69	2.25 ± 0.77 (cystic part) 1.50 ± 0.88 (solid part)	2.78 ± 0.45	H and FU	82.1[*] 90[†]	76.5[*] 83.3[†]	1.80 1.66
Kilickesmez [18] et al.	52	67	1.5	0, 500, 1000	–	–	–	–	–	–	1.06 ± 0.39	–	2.94 ± 0.20 (simple) 1.71 ± 0.38 (haemorrhagic)	H, I, and FU	NR	NR	–
Wang et al. [14]	83	85	3	0, 500 0, 800	0.88 ± 0.15 1.09 ± 0.20	1.70 ± 0.32 1.85 ± 0.40	1.14 ± 0.16 1.31 ± 0.34	–	–	–	–	–	–	H	95.9[‡]	94.4[‡]	1.28
Paudyal et al. [15]	32	32	1.5	0, 300, 1000	–	1.59 ± 0.55	–	–	6.72 ± 1.85	–	–	–	–	H	NR	NR	–
Rosenkrantz et al. [19]	57	57	1.5	0, 400	–	1.59 ± 0.57 (high grade) 2.24 ± 0.50 (low grade)	–	–	–	–	–	–	–	H	88.5§	64.5§	2.17
				0, 800		1.28 ± 0.48 (high grade) 1.85 ± 0.40 (low grade)									65.4§	96§	1.20
Sandrasegaran et al. [11]	42	69	1.5	0, 800	–	1.85 ± 0.23 (any grade) 1.77 ± 0.20 (high grade) 1.95 ± 0.25 (low grade)	–	–	1.97 ± 0.14	–	–	2.02 ± 0.12	2.76 ± 0.32	H, I and FU	100[*] 94‖	88[*] 87‖	2.19 2.22
Doğanay et al. [20]	58	67	1.5	100 600 1000	–	–	–	–	–	2.63 ± 0.33 2.55 ± 0.49 2.40 ± 0.15	2.88 ± 0.50 2.21 ± 0.63 1.67 ± 0.45	–	3.34 ± 0.52 3.20 ± 0.54 2.80 ± 0.54	H and I	93.7[*] 90.6[*] 93.7[*]	31.4[*] 48.5[*] 45.7[*]	3.4 2.9 2.4
Razek et al. [21]	52	54	1.5	0, 800	1.65 ± 0.26	1.74 ± 0.12	1.44 ± 0.12	–	–	2.10 ± 0.10	–	–	–	H	89[*] 89¶	89[*] 83¶	1.84 1.62
Inci et al. [22]	105	105	1.5	0, 500, 1000	0.90 ± 0.16	1.23 ± 0.13	1.41 ± 0.09	–	–	1.61 ± 0.10	–	–	3.09 ± 0.15 (Bosniak I) 2.37 ± 0.37 (Bosniak II) 2.34 ± 0.29 (Bosniak III)	H, I and FU	NR	NR	–

ADC = apparent diffusion coefficient; RCC = renal cell carcinoma; NR = not reported; H = histology; I = imaging (ultrasound and/or conventional cross-sectional imaging); FU = clinical and/or imaging follow-up.

[*] Diagnosis of RCC (among all lesions).

[†] Diagnosis of solid RCC (among solid enhancing lesions).

[‡] Diagnosis of clear cell RCC versus non–clear cell RCC.

§ Diagnosis of high-grade clear cell RCC versus low-grade clear cell RCC.

‖ Diagnosis of cystic RCC versus benign cysts.

¶ Diagnosis of clear cell plus papillary RCC versus other RCC subtypes.

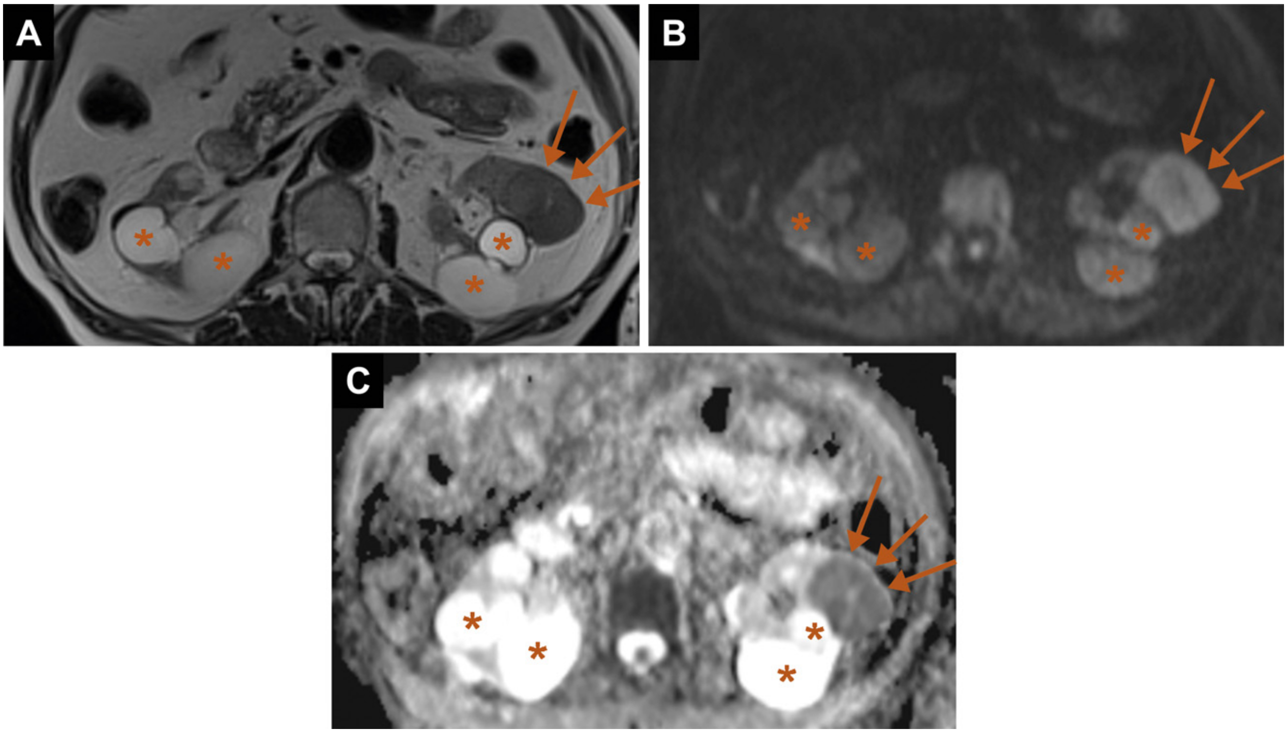

Fig. 1 – Magnetic resonance imaging (MRI) of an 82-yr-old man with flank pain and chronic renal failure performed on a 1.5-T MRI unit. (A) Axial high-resolution T2-weighted MRI shows a focal mass at the midlevel of left kidney (arrows) with hypointense signal intensity and multiple bilateral hyperintense focal lesions (asterisks), corresponding to renal cysts. (B) On axial diffusion-weighted MRI at a b-value of 900 s/mm^2, the focal mass (arrows) is hyperintense compared with the simple cysts (asterisks). (C) On the corresponding apparent diffusion coefficient map, the focal mass (arrows) is visualised as a hypointense lesion with impeded diffusion compared with the simple cysts, which appear bright (asterisks). Histology after left partial nephrectomy revealed a Fuhrman grade II clear cell renal cell carcinoma.

3.3. Prostate cancer

3.3.1. Detection and localisation

The current standard procedure for PCa detection is transrectal ultrasound (TRUS)–guided systematic biopsy [23]. Although TRUS provides a good depiction of the peripheral zone (PZ), evaluation of the transition zone (TZ) and the more anterior region of the prostate remains a major challenge. In addition, free-hand random biopsies are subject to sampling error. In recent years, PCa detection and staging has improved using conventional T2-weighted MRI (T2w-MRI); however, in a high number of cases the differentiation between PCa and normal prostatic tissue can be impossible not only in the TZ but also in the PZ (Fig. 2).

Initial research on the usefulness of DW-MRI in this particular setting has primarily focused on PZ because most

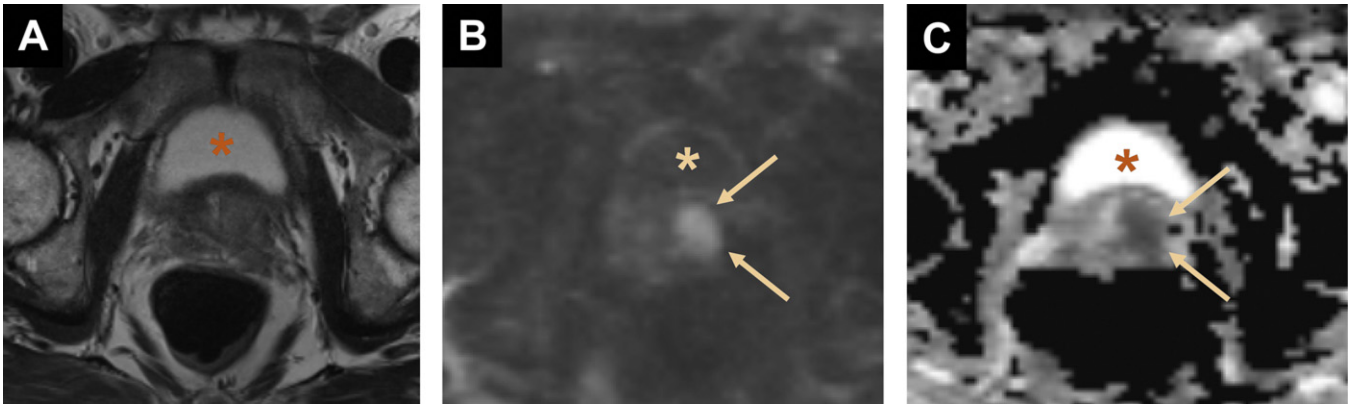

Fig. 2 – Magnetic resonance imaging (MRI) of a 63-yr-old man with known prostate cancer performed on a 3-T MRI unit. (A) Axial high-resolution T2-weighted MRI shows low signal intensity areas in the whole prostate, predominantly in the left lobe; exact delineation of the tumour is not possible. (B) Axial diffusion-weighted MRI at the same level acquired at a b-value of 1000 s/mm^2 shows a hyperintense lesion (arrows) in the peripheral zone of the left prostate lobe with extension into the ipsilateral transition zone at the midlevel. Asterisk identifies bladder. (C) On the corresponding apparent diffusion coefficient (ADC) map, the tumour is visualised as a hypointense lesion (arrows) with an ADC value of 0.66 × 10^{-3} mm^2/s. Histology after radical prostatectomy confirmed unilateral prostate cancer with a Gleason score of 8. Asterisk identifies bladder.

prostate tumours are located there. When DW-MRI is combined with T2w-MRI, sensitivity and specificity increase substantially, ranging from 71% to 89% and from 61% to 91%, respectively, compared with from 49% to 88% and from 57% to 84%, respectively, for either modality alone, resulting also in a lower interobserver variability [24–30]. In several publications [25,31–37], PCa tissue showed significantly lower ADC values than normal PZ tissue with minimal overlap within most single studies. However, due to heterogeneity in technical parameters and postprocessing, the reported sensitivities and specificities varied considerably, ranging from 40% to 95%. Due to the lack of standardisation in DW-MRI protocols, absolute ADC values are influenced by several sources of variability, mainly the choice of the underlying b-values. Therefore, at present, a reliable cut-off ADC value for malignancy that can be used universally in clinical routine and allows comparison between studies is difficult to identify. Table 2 lists recent publications on this topic [31–49].

Detection of PCa in the TZ is more difficult due to the high cellularity observed in both benign prostatic hyperplasia (BPH) and tumour. Although DW-MRI also performs better than T2w-MRI in the TZ, there is a large overlap between PCa and BPH, limiting its usefulness for the individual patient (Table 2). This was recently reconfirmed in a study comparing 38 tumour foci, 38 nodules of stromal hyperplasia, and 38 nodules of glandular hyperplasia in the TZ, where significant ADC differences could be observed between groups but a substantial overlap was evident [47].

Patients with one or more negative prostate biopsy sets and a high suspicion of PCa would profit most from a noninvasive imaging modality such as DW-MRI. In a study of 43 patients with previously negative TRUS-guided prostate biopsy and persistently elevated prostate-specific antigen (PSA) levels, DW-MRI at 3 T performed before a further TRUS-guided biopsy could detect PCa in 17 (39.5%) patients, whereas T2w-MRI could detect PCa in only 6 of them [50]. The sensitivity rates reported in this study are lower than those reported in previous studies, possibly because of a relatively higher incidence of TZ tumour (76.4%), which is traditionally challenging to detect with any imaging modality. In addition, the suspicious PCa foci detected on the ADC map might have been mistargeted with TRUS guidance. Prostate biopsy under MRI guidance would instead maximise the advantage of improved PCa detection and localisation with DW-MRI. However, there is no current consensus on the optimal technique, and the clinical experience is still limited [51].

3.3.2. *Characterisation*

Several studies have consistently demonstrated an inverse correlation between ADC values and Gleason score as well as tumour risk category of commonly accepted criteria, especially for PZ tumours [45,52–56]. Lower ADC values seem to be associated with higher Gleason scores, probably due to higher cellular density in poorly differentiated tumours, resulting in more impeded diffusion of water molecules. The main common shortcoming common to all these studies is the substantial overlap between ADC values and different Gleason scores, so that the routine use of DW-MRI to define tumour aggressiveness for the individual patient cannot yet be recommended.

3.3.3. *Local staging*

Currently, DW-MRI cannot accurately predict extracapsular extension due to frequently encountered image distortion and artefacts, and lower spatial resolution compared with T2w-MRI [57]. However, DW-MRI holds promise to improve the prediction of seminal vesicle invasion, which is still considered a major negative prognostic factor [58]. An initial study including 166 patients conducted on a 3-T scanner reported that DW-MRI used in conjunction with T2w-MRI significantly improved specificity (from 87% to 97%) and accuracy (from 87% to 96%) for the prediction of seminal vesicle invasion compared with T2w-MRI alone [59]. A subsequent study including 283 patients with 39 cases of seminal vesicle invasion confirmed these results using quantitative analysis based on ADC values [60]. Mean ADC values of tumour-bearing seminal vesicles were significantly lower than those of tumour-free seminal vesicles, with an area under the curve (AUC) of T2w-MRI plus DW-MRI (0.897) significantly higher ($p < 0.05$) than that of T2w-MRI alone (0.779). These encouraging results need further validation in larger studies.

3.3.4. *Predicting and monitoring treatment response*

3.3.4.1. Active surveillance. Both PSA and its kinetics as well as repeat prostate biopsy strategies due to inherent sampling error and misgrading remain suboptimal in the monitoring of patients on active surveillance [23]. In light of the earlier mentioned ability to predict tumour aggressiveness, DW-MRI might be useful in this setting because it would allow selecting candidates and monitoring changes during follow-up in a noninvasive manner. In a study of 86 patients on active surveillance followed for a median of 29 mo, lower tumour ADC values were significantly associated with both adverse findings on repeat biopsy and shorter time to radical treatment on univariable analysis [61]. These findings were corroborated by the same investigators in two subsequent studies [62,63].

3.3.4.2. Radical prostatectomy. Two studies demonstrated the potential of DW-MRI to serve as a predictive biomarker for recurrence following radical prostatectomy for clinically localised PCa. In one small study including 12 patients with biochemical recurrence after surgery [64], the AUC for the Partin tables plus T2w-MRI and qualitative DW-MRI staging (0.79) was significantly greater than the AUC for the Partin tables alone (0.67) in predicting biochemical recurrence. In another study including 30 patients with biochemical recurrence [65], a multivariable analysis identified tumour ADC as the only independent predictive factor of biochemical recurrence among established preoperative clinical and histologic parameters, with an AUC of 0.755. However, due to the retrospective design, small sample size, and relatively short follow-up, these data should be interpreted with caution. Biochemical recurrence depends on several factors, among which specific tumour biology plays a major role.

Table 2 – Recently published studies with ≥15 prostate cancer cases reporting apparent diffusion coefficient values for benign and malignant tissue in different regions of the prostate

Study	No. of patients with PCa	No. of controls	Imaging			ADC value, × 10^{-3} mm^2/s (mean ± standard deviation)						Reference standard	Sensitivity, %	Specificity, %	Threshold ADC value, × 10^{-3} mm^2/s)
			Field strength, T	b-values, s/mm^2	Coil	PZ tumour	TZ tumour	PZ patient	TZ patient	PZ control	TZ control				
Sato et al. [36]	23	6	1.5	0, 300, 600	PA	1.08 ± 0.39	1.13 ± 0.42	1.80 ± 0.41	1.58 ± 0.37	1.93 ± 0.24	1.68 ± 0.26	Bx	NR	NR	–
Pickles et al. [33]	49	9	3	0, 500	PA	1.38 ± 0.32		1.95 ± 0.50	–	1.60 ± 0.25	1.27 ± 0.14	Bx and I	NR	NR	–
Gibbs et al. [31]	62	–	3	0, 500	PA	1.19 ± 0.26		1.64 ± 0.21	–	–	–	Bx and I	82§	78§	1.50
Manenti et al. [35]	19	10	1.5	0, 125, 250, 375, 500	PA	0.96 ± 0.17		1.98 ± 0.23	1.51 ± 0.12	2.08 ± 0.22	1.57 ± 0.12	Bx and I	NR	NR	–
Kumar et al. [38]	23	7	1.5	0, 250, 500, 750, 1000	PA + ER	0.98 ± 0.22	1.00 ± 0.25	1.34 ± 0.30‡	1.12 ± 0.15‡	1.68 ± 0.31	1.07 ± 0.25	Bx and I	73 §	74 §	1.17
deSouza et al. [39]	30	–	1.5	0, 300, 500, 800	ER	1.30 ± 0.30	–	1.71 ± 0.16	1.46 ± 0.14	–	–	Bx and I	86.7‖ 60¶	72.2‖ 76¶	1.60 1.39
Kim et al. [34]	35	–	3	0, 1000	PA	1.32 ± 0.24	1.37 ± 0.29	1.97 ± 0.25	1.79 ± 0.19	–	–	RP	94‖ 90¶	91‖ 84¶	1.67 1.61
Reinsberg et al. [37]	42	–	1.5	0, 300, 500, 800	ER	1.03 ± 0.18	–	1.51 ± 0.27	1.31 ± 0.20	–	–	Bx and I	93.3** 67.3††	57.4** 59.9††	1.26
Tamada et al. [32]	90	125	1.5	0, 800	PA	1.02 ± 0.25	0.94 ± 0.21	–	–	1.80 ± 0.27	1.34 ± 0.14	Bx and I	NR	NR	–
Kim et al. [40]	47	–	1.5	0, 1000	PA + ER	0.99 ± 0.21	0.96 ± 0.14	1.57 ± 0.34	1.44 ± 0.31	–	–	RP	98‖ 81¶	81‖ 87¶	NR
Kitajima et al. [41]	26	–	1.5	0, 1000 0, 2000	PA	0.82 ± 0.27 0.61 ± 0.19	–	1.69 ± 0.23 1.01 ± 0.14	–	–	–	Bx and I	NR	NR	–
Zelhof et al. [42]	32	–	3	0, 500	PA	1.45 ± 0.27	–	1.90 ± 0.33	–	–	–	RP	81‖	78‖	1.62
Gibbs et al. [43]	20	–	3	0, 500	PA	1.43 ± 0.19	–	1.88 ± 0.22	–	–	–	RP	NR	NR	–
Wang et al. [44]	38	33*	1.5	0, 300, 600	PA	0.49 ± 0.13	–	1.26 ± 0.27	0.87 ± 0.27	–	–	RP or Bx	NR	NR	–
Woodfield et al. [45]	57	–	1.5	0, 1000	PA + ER	0.74 ± 0.15	–	1.48 ± 0.29	–	–	–	Bx and I	NR	NR	–
Kim et al. [46]	48	–	3	0, 1000 0, 2000	PA	1.19 ± 0.33 1.58 ± 0.41	1.21 ± 0.23 1.63 ± 0.30	2.04 ± 0.34 2.61 ± 0.36	1.77 ± 0.30 2.23 ± 0.37	–	–	RP	88§ 71§	90§ 92§	NR
Oto et al. [47]	49	–	1.5	0, 1000, 1500	PA + ER	–	1.05 ± 0.21	–	1.27 ± 0.21 (SH) 1.73 ± 0.28 (GH)	–	–	RP	38‡‡	90‡‡	NR
Langer et al. [48]	24	–	1.5	0, 600	PA + ER	1.28 (0.85–1.69)†	–	1.56 (1.05 -2.09)†	–	–	–	RP	NR	NR	–
Yamamura et al. [49]	21	–	1.5	50, 400, 800	PA + ER	0.96 ± 0.24	–	1.65 ± 0.32	–	–	–	Bx	92	93	1.21

PCa = prostate cancer; ADC = apparent diffusion coefficient; PZ = peripheral zone; TZ = transition zone; PZ patient and TZ patient = refers to nonmalignant tissue in patients with PCa; PZ control and TZ control = refers to controls with no PCa; PA = phased array; Bx = prostate biopsy (including transurethral resection); NR = not reported; I = conventional T2-weighted magnetic resonance imaging; ER = endorectal; RP = radical prostatectomy specimen; SH = stromal hyperplasia; GH = glandular hyperplasia.

* Subjects with benign prostatic hyperplasia.

† Median and range.

‡ Subjects with negative Bx.

§ Tumour versus no tumour.

‖ PZ tumour versus PZ patient.

¶ PZ tumour versus TZ patient.

** Voxel containing ≥70% tumour.

†† Voxel containing ≥30% tumour.

‡‡ TZ tumour versus TZ patient (for SH).

Therefore, in future studies the information provided by functional imaging should be incorporated into predictive models including numerous variables.

3.3.4.3. Detection of local recurrence after treatment with curative intent. After radiation therapy, prostate biopsy is considered the gold standard to diagnose locally recurrent PCa, but it is associated with substantial false-negative and positive rates [66]. T2w-MRI is often challenging in these patients due to radiation-induced changes in prostatic tissue with a resulting low sensitivity for the detection of recurrent PCa. Despite the additive value of MR spectroscopy in increasing the diagnostic accuracy of endorectal MRI [67], there is still need for improvement (eg, by faster and more available techniques with easier image interpretation). Two small studies [68,69] showed that DW-MRI combined with T2w-MRI (in one study) and with delayed contrast-enhanced (DCE) MRI and T2w-MRI (in the other) significantly improved the diagnostic performance of each modality alone in detecting local recurrence after external-beam radiation therapy.

A single study evaluated the role of DW-MRI in detecting local recurrence after high-dose-rate brachytherapy in a multiparametric context including also conventional MRI and DCE-MRI [70]. Sensitivity was highest for multiparametric MRI (77%), followed in decreasing order by DW-MRI (68%), DCE-MRI (50%), and T2w-MRI (27%). Specificity was slightly lower for multiparametric MRI (92%) compared with the individual sequences (range: 95–99%).

Whole-gland ablation with high-intensity focussed ultrasound (HIFU) is an emerging alternative option for the treatment of selected patients with localised PCa, although robust long-term oncologic follow-up data are lacking [71]. A major obstacle to its applicability remains establishing treatment efficacy. Ablation of prostatic tissue leads to coagulation necrosis and cavitation effects, resulting in a diffuse low signal intensity in T2w-MRI sequences, thus hampering the identification of residual/recurrent tumour [72]. In the only available study including 27 PCa patients with biochemical recurrence after HIFU ablation, DW-MRI combined with T2w-MRI had higher specificity but lower sensitivity compared with DCE-MRI in predicting local recurrence [73]. An attractive application of DW-MRI may be the local monitoring of patients undergoing focal therapy of the prostate, which is becoming increasingly popular for the minimally invasive treatment of low-risk PCa [74].

The literature search did not reveal any publications on the use of DW-MRI to detect local recurrence after radical prostatectomy. Further studies are eagerly awaited to define the optimal imaging technique to evaluate local treatment outcome after various curative approaches.

3.4. Bladder cancer

3.4.1. Detection

In patients with gross haematuria or under follow-up after treatment of non–muscle-invasive BCa, the differentiation between benign and malignant lesions of the bladder could avoid the need for invasive procedures, provided that upper

Table 3 – Published studies reporting apparent diffusion coefficient values for benign and malignant lesions of the bladder

Study	No. of patients	No. of controls	Imaging			ADC value, × 10^{-3} mm^2/s, mean ± standard deviation				Reference standard	Sensitivity, %*	Specificity, %*	Threshold ADC value, × 10^{-3} mm^2/s
			Field strength, T	b-values, s/mm^2	Coil	Malignant lesions	Benign lesions	Bladder patient	Bladder control				
Matsuki et al. [77]	15	–	1.5	0, 800	PA	1.18 ± 0.21	–	2.27 ± 0.24	–	H	NR	NR	–
El-Assmy et al. [78]	43	–	1.5	0, 800	PA	1.40 ± 0.51	–	2.29 ± 0.78	–	H	NR	NR	–
Kiliçkesmez et al. [79]	14	50	1.5	0, 500, 1000	PA	0.94 ± 0.18	–	–	2.08 ± 0.22	H and I	NR	NR	–
Ceylan et al. [76]	59	–	1.5	NR	PA	1.05 ± 0.22	1.73 ± 0.12	1.83 ± 0.18	–	CS and H	97.6	96	NR
Avcu et al. [80]	83	20	1.5	0, 500, 1000	PA	1.07 ± 0.26	1.80 ± 0.19	–	2.01 ± 0.11	CS	100	76.5	NR

ADC = apparent diffusion coefficient; Bladder patient = refers to normal-looking bladder tissue in patients with bladder lesions; Bladder control = refers to bladder tissue in controls with no bladder lesions; PA = phased array; H = histology; NR = not reported; I = conventional T2-weighted magnetic resonance imaging; CS = cystoscopy.

* Diagnosis of malignant versus benign lesions.

tract tumours are excluded. In a prospective study including 130 patients with gross haematuria, DW-MRI had 98.1% specificity and 92.3% sensitivity in discriminating a total of 106 malignant cases from 14 benign conditions [75]. However, the diagnostic performance of T2w-MRI in that study was only slightly lower than that of DW-MRI, likely due to the large mean size of the lesions. A smaller study including 59 patients with gross haematuria or under follow-up after previous BCa showed 97.6% specificity and 96% sensitivity in discriminating 34 malignant lesions from 9 benign conditions [76]. Mean ADC values for malignant lesions were significantly lower than those for benign conditions and normal bladder wall. Details of all published studies on this topic are specified in Table 3 [76–80]. In most studies, the exact criteria to define bladder tumour and abnormal but nonmalignant conditions were not reported. Therefore, the value of DW-MRI as a first-line diagnostic test to differentiate tumour from benign disease of the bladder needs further research.

3.4.2. Local staging

Distinguishing non–muscle-invasive from muscle-invasive BCa is crucial for patient management because treatment options differ considerably, ranging from radical surgery to bladder-sparing options [81]. The true advantage of any imaging technique for local staging is debatable because transurethral resection (TUR) cannot be avoided to obtain histologic diagnosis. However, TUR can underestimate the local extent of the disease in a significant proportion of cases [82]. Consequently, the additional information given by preoperative imaging may be helpful.

Currently, BCa staging is usually performed using T2w-MRI and dynamic CE-MRI (DCE-MRI), which are apparently superior to CE-CT. However, upstaging seems to be a major drawback because conventional T2w-MRI cannot accurately differentiate the various bladder wall layers [83]. In addition, this technique requires gadolinium-based contrast agents, which are contraindicated in patients with impaired renal function. To overcome these limitations, several recent studies have investigated the use of DW-MRI in the work-up of BCa (Fig. 3 and 4).

In one study including 40 patients with 52 bladder tumours, DW-MRI combined with T2w-MRI was able to differentiate between T1 or lower tumours from T2 or higher tumours with 96% accuracy, and between T2 or lower tumours from T3 to T4 tumours with 92% accuracy

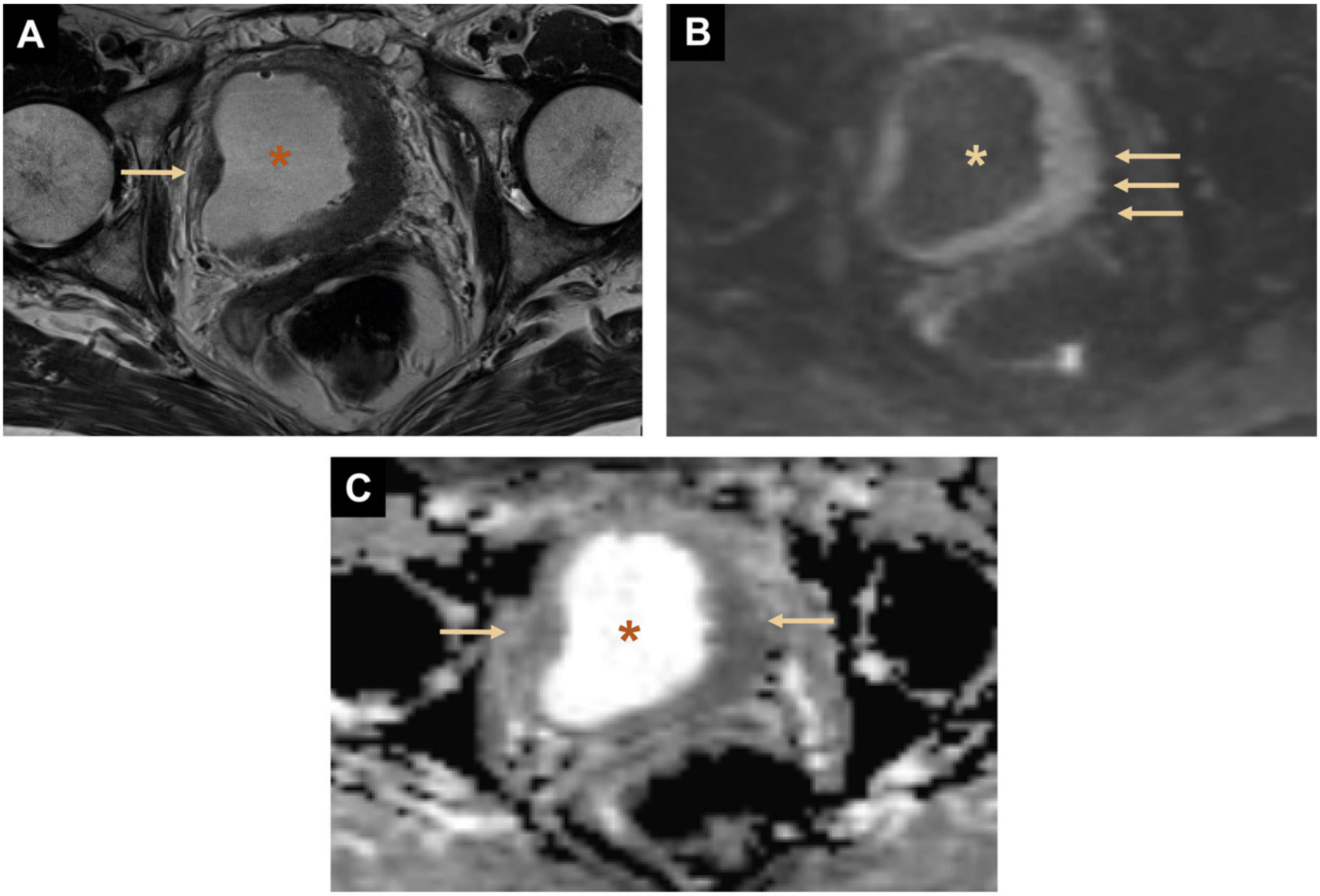

Fig. 3 – Magnetic resonance imaging (MRI) of a 65-yr-old woman with known bladder cancer performed on a 3-T MRI unit. (A) Axial high-resolution T2-weighted MRI shows large hypointense thickening of the left bladder wall and a small circumscribed focal thickening of the right bladder wall (arrow). Asterisk identifies bladder. (B) Axial diffusion-weighted MRI at a b-value of 1000 s/mm^2 shows hyperintense thickening of the bladder wall on both sides with extension into the perivesical fat only on the left side (arrows). Asterisk identifies bladder. (C) On the corresponding apparent diffusion coefficient (ADC) map, both tumours are visualised as hypointense lesions (arrows) with an ADC value of 0.90 × 10^{-3} mm^2/s. Histology after radical cystectomy confirmed a pT3a urothelial carcinoma of the bladder. Asterisk identifies bladder.

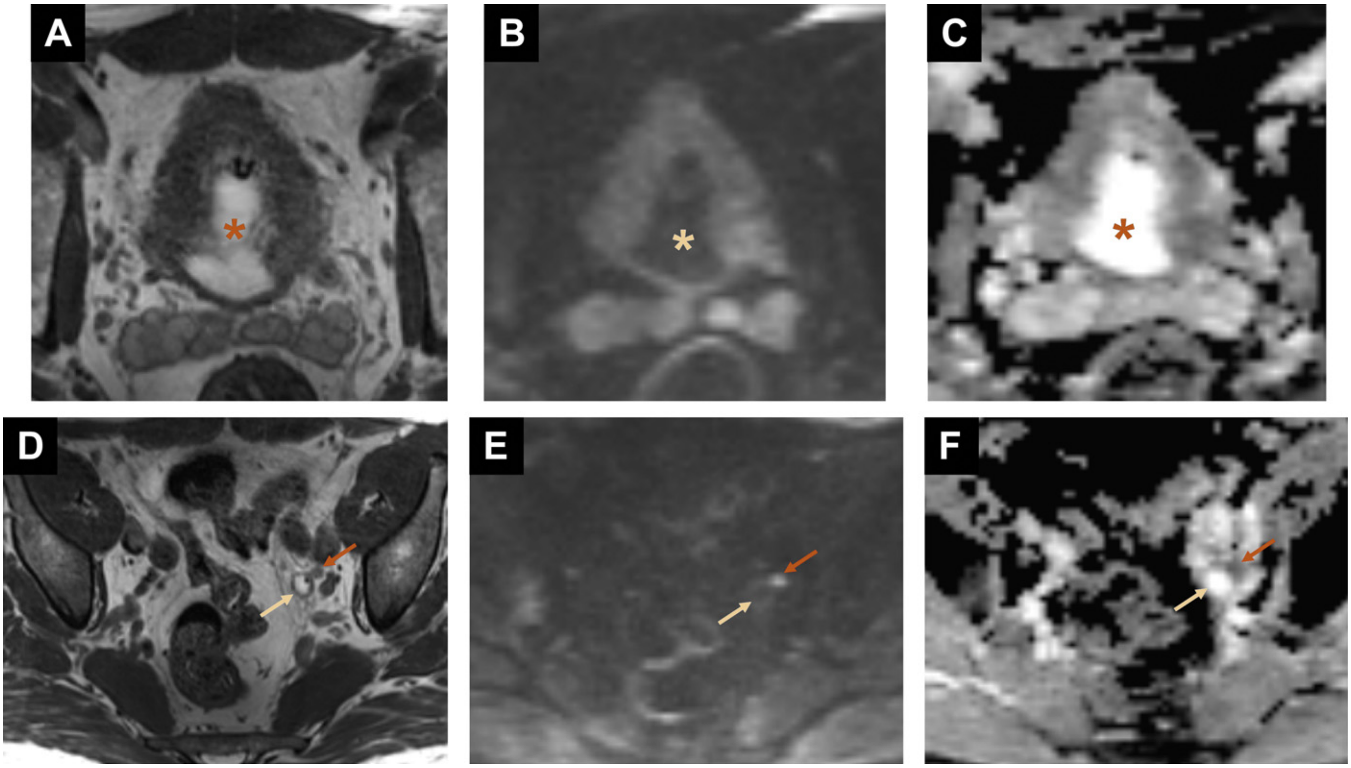

Fig. 4 – Magnetic resonance imaging (MRI) of a 63-yr-old man with known bladder cancer performed on a 3-T MRI unit. (A) Axial T2-weighted MRI shows extensive hypointense semicircumferential bladder wall thickening, with suspicious invasion into the perivesical fat (arrows). Asterisk identifies bladder. (B) Axial diffusion-weighted MRI at a b-value of 1000 s/mm^2 shows hyperintense thickened bladder wall without signs of infiltration into the perivesical fat. Asterisk identifies bladder. (C) On the corresponding apparent diffusion coefficient (ADC) map, the bladder wall has an ADC value of 0.96 × 10^{-3} mm^2/s. Asterisk identifies bladder. (D) Axial T2-weighted MRI at the level of fossa Marcille shows a dilated left-sided ureter (white arrow) with a small (3 mm) adjacent lymph node (red arrow). (E) Axial diffusion-weighted MRI at a b-value of 1000 s/mm^2 at the same level as in (D) shows the lymph node as a small hyperintense lesion (red arrow), whereas the dilated ureter (white arrow) is not visible. (F) On the corresponding ADC map, the lymph node (red arrow) shows impeded diffusion with an ADC value of 0.94 × 10^{-3} mm^2/s, whereas the dilated ureter (white arrow) reveals a bright signal with a high ADC value due to increased diffusion. Histology after radical cystectomy and extended template pelvic lymph node dissection confirmed a pT2 urothelial carcinoma of the bladder with a single lymph node metastasis of 1 mm in a 3-mm node.

based on morphologic findings at high b-values, increasing the performance of T2w-MRI alone. Overall T-stage accuracy increased from 67% using T2w-MRI alone to 88% when DW-MRI was added. This combination was superior to T2w-MRI plus DCE-MRI (79% accuracy) [84]. In another study including 106 BCa patients, an inferior accuracy of 63.6% for differentiating non–muscle-invasive from muscle-invasive tumours and of 69.6% for differentiating organ-confined from non–organ-confined tumours was observed when DW-MRI alone was evaluated, although accuracy for T2w-MRI alone was even worse (6.1% and 15.1%, respectively) [83]. This discrepancy may be due to the better image quality achieved in the former study [82], where diffusion-sensitising gradients were applied in the three orthogonal directions and 14 signal averages were acquired with a 4-mm-slice thickness, compared with the latter study [83] in which monodirectional gradients were applied using 7 signal averages and a 5-mm-slice thickness. In a smaller study including 18 patients with histologically confirmed BCa, upstaging decreased from 21% for unenhanced T1w- and T2w-MRI alone to 16% for CE-MRI and to only 5% by using DW-MRI in addition to T1w- and T2w-MRI [85].

Notably, in all these studies, imaging was performed before TUR. It is well known that post-TUR inflammatory changes negatively affect the staging accuracy of conventional morphologic imaging. However, functional imaging does not apparently overcome this interpretative pitfall.

3.4.3. *Characterisation*

Histologic grade of BCa is a fundamental prognostic factor. Attempts have been made to define tumour grade noninvasively using DW-MRI. ADC values were found to predict histologic grade in two recent studies. In the previously mentioned study [84], mean ADC values (b-values: 0 and 1000s/mm^2) for G3 tumours ($0.81 \pm 0.11 \times 10^{-3}$ mm^2/s) were significantly lower ($p < 0.01$) than those for G1 ($1.29 \pm 0.21 \times 10^{-3}$ mm^2/s) and G2 tumours ($1.13 \pm 0.24 \times 10^{-3}$ mm^2/s). Similar results were reported in a second study [80] with mean ADC values (b-values: 0, 500, and 1000s/mm^2) for high-grade tumours ($0.918 \pm 0.20 \times 10^{-3}$ mm^2/s) significantly ($p < 0.01$) lower than those for low-grade tumours ($1.28 \pm 0.18 \times 10^{-3}$ mm^2/s). However, ADC values showed a substantial overlap in high- and low-grade tumours, thus limiting the usefulness of DW-MRI for the individual patient.

3.4.4. *Treatment monitoring*

Predicting the response to induction chemotherapy in patients with muscle-invasive BCa is fundamental to determine whether salvage radical surgery is required. One study explored the role of DW-MRI performed at 1.5 T with b-values of 0, 500, and 1000s/mm^2 in assessing the response to induction chemoradiotherapy in 20 patients with muscle-invasive BCa [86]. A significantly higher specificity and accuracy (92% and 80%) compared with T2w-MRI (45% and 44%) and DCE-MRI (18% and 33%) to predict complete response evaluated by histopathology was observed. If confirmed by further experience, these data suggest the potential of DW-MRI to serve as a biomarker of treatment response in the context of neoadjuvant chemotherapy strategies to radical cystectomy, where histopathology is the reference standard, thereby eventually allowing individualised treatment.

3.5. *Pelvic lymph node staging*

The presence of pelvic LN metastases in patients with PCa and BCa is of major prognostic relevance and decisive for treatment planning [87,88]. LN staging is routinely performed by conventional cross-sectional imaging, and it is only based on dimensional criteria, with a threshold of 8–10 mm in short axis diameter or clusters of smaller regional LNs most commonly used [89]. This is far from optimal because tumour deposits are present in roughly 25% of surgically treated PCa and BCa patients with normal-size LNs on preoperative imaging [90,91], and LNs can be enlarged due to inflammatory/reactive changes (Fig. 4).

DW-MRI has the potential to discriminate malignant from benign LNs because the former are expected to have an impeded diffusion due to high cellularity, resulting in low ADC values. The specific literature is still limited, however, and with contrasting results. In a study of 29 PCa patients with a total of 118 LNs evaluated by DW-MRI at 1.5 T, highly significantly lower ($p < 0.0001$) ADC values were observed in metastatic versus nonmetastatic LNs ($1.07 \pm 0.23 \times 10^{-3}$ mm^2/s vs $1.54 \pm 0.25 \times 10^{-3}$ mm^2/s, respectively) using either histology or clinical follow-up as the standard of reference [92]. When using a cut-off value of 1.30×10^{-3} mm^2/s, sensitivity was 86%, specificity 85%, and accuracy 86% to discriminate LN status. These observations were confirmed in a subsequent smaller study by the same group including 14 PCa patients evaluated with DW-MRI at 1.5 T and (11)C-choline-positron emission tomography (PET)/CT [93]. Histopathology was used as the standard of reference in only five patients. ADC values were significantly lower and standardised uptake value (SUV) significantly higher in malignant than in benign LNs (ADC: $1.09 \pm 0.23 \times 10^{-3}$ mm^2/s vs $1.60 \pm 0.24 \times 10^{-3}$ mm^2/s; SUV: 1.82 ± 0.57 vs 4.68 ± 03.12; $p < 0.0001$, respectively). At a cut-off of 1.43×10^{-3} mm^2/s, sensitivity was 96.3%, specificity 78.6%, and accuracy 83.6%. A moderate but highly significant inverse correlation ($r = -0.5144$; $p < 0.0001$) between ADC values and SUV was observed. Thus the ADC value in DW-MRI may serve as a potential biomarker for LN status. In these studies large and small LNs were included, the smallest LN size considered was a short axis diameter of 5 mm, and none were able to define the negative predictive value of DW-MRI.

In contrast, disappointing results for DW-MRI at 1.5 T in detecting LN metastases were found in another study including 36 high-risk PCa patients treated with radical prostatectomy and extended pelvic LN dissection, with a sensitivity and a positive predictive value of only 18.8% and 46.2%, respectively, in a LN region-based analysis [94]. These figures increased to 42.9% and 60%, respectively, in a patient-based analysis. However, this poor performance may be due to the 53.1% positive LNs containing only micrometastases or isolated tumour deposits, albeit in some cases macrometastases were also missed. In this study, ADC values were not reported, making it difficult to compare data with previously published research.

A combination of DW-MRI with ultrasmall superparamagnetic particles of iron oxide (USPIO) showed 90% accuracy in detecting metastases even in normal-size LNs of PCa and BCa patients based on visual assessment, thereby facilitating the approach of this challenging diagnostic problem [95]. In this study a meticulous pelvic LN dissection allowed correct assessment of the negative predictive value, which was reported to be 94% per pelvic side. Although these results were encouraging, larger studies are needed to confirm them; unfortunately, USPIO is currently unavailable.

3.6. *Future perspectives*

The major prerequisite for further advances in DW-MRI is the standardisation of this technique. Image acquisition and sequence parameters of different scanner platforms have to be defined and implemented, thus enabling comparison of imaging studies between different centres. Efforts are strongly required to avoid reading/interpretation bias both in the qualitative and quantitative analysis, thus minimising the interobserver variability. Initial attempts have been made to standardise DW-MRI for various organs and, specifically, multiparametric MRI for PCa detection and localisation [96,97]. The achievement of these goals would enable the conduct of high-quality multicentre clinical trials, which are required for further validation of this promising technique, and also the rapid dissemination of this technique to nonacademic community-based institutions by reducing the individual learning curve. Finally, the applicability of this technique on a large scale may be facilitated by the lack of additional costs compared with conventional cross-sectional imaging. Costs could actually be reduced because contrast medium administration may be avoided in selected cases.

Definition of cut-off values for the noninvasive differentiation between benign and malignant tumours and their LN metastases, and eventually for discrimination of various histologic subtypes and grading, might allow individualised patient management.

In addition, DW-MRI could serve as a biomarker for predicting and monitoring treatment response in patients with genitourinary tumours undergoing targeted therapies. For example, antiangiogenic therapy is an established treatment for metastatic RCC [98]. Because these new agents do not lead to an immediate reduction in tumour size, newer imaging techniques able to detect early changes in tumour metabolism under treatment are warranted. DW-MRI has the potential to show such microstructural changes before dimensional alterations, providing different

ADC values at different dose levels and days of therapy and thus acting as a biomarker of early drug activity [5].

The current trend is toward the use of multiparametric MRI, combining conventional and functional MRI, including DCE-MRI, DW-MRI, MR spectroscopy, arterial spin labelling, and blood oxygen level–dependent MRI, with first studies mainly applied to the prostate [99]. However, the multiparametric approach is time consuming and requires special software, contrast medium, and high expertise. Therefore, future studies ideally will determine which technique or combination of techniques will best answer the clinical questions in daily routine to ultimately optimise patient care.

4. Conclusions

Although CE-CT and conventional MRI are still standard techniques for the work-up of genitourinary tumours, DW-MRI has shown the potential to address some unresolved clinical needs due to its ability to explore microstructural tissue abnormalities at an early time point. DW-MRI is a reasonable alternative to CE imaging to detect and characterise focal renal lesions especially in patients with impaired renal function. DW-MRI improves the detection and localisation of PCa and may have a role in monitoring patients under active surveillance and after local curative therapy. DW-MRI may improve staging of BCa when used in addition to T2w-MRI. Finally, it has the potential to discriminate malignant from benign pelvic LNs. Standardisation of technical parameters and improvement in image analysis and interpretation will enable the validation of this promising technique.

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Study concept and design: Giannarini, Thoeny.
Acquisition of data: Giannarini, Petralia, Thoeny.
Analysis and interpretation of data: Giannarini, Petralia, Thoeny.
Drafting of the manuscript: Giannarini, Petralia, Thoeny.
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References

[1] Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497–505.

[2] Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR imaging of the brain. Radiology 2000;217:331–45.

[3] Merino JG, Warach S. Imaging of acute stroke. Nat Rev Neurol 2010;6:560–71.

[4] Thoeny HC, De Keyzer F. Extracranial applications of diffusion-weighted magnetic resonance imaging. Eur Radiol 2007;17: 1385–93.

[5] Thoeny HC, Ross BD. Predicting and monitoring cancer treatment response with diffusion-weighted MRI. J Magn Reson Imaging 2010;32:2–16.

[6] Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Radiology 2003;226:24–8.

[7] Thoeny HC, De Keyzer F, Boesch C, Hermans R. Diffusion-weighted imaging of the parotid gland: influence of the choice of b-values on the apparent diffusion coefficient value. J Magn Reson Imaging 2004;20:786–90.

[8] Thoeny HC, De Keyzer F. Diffusion-weighted MR imaging of native and transplanted kidneys. Radiology 2011;259:25–38.

[9] Zhang J, Tehrani YM, Wang L, Ishill NM, Schwartz LH, Hricak H. Renal masses: characterization with diffusion-weighted MR imaging—a preliminary experience [published correction appears in Radiology 2010;255:1011]. Radiology 2008;247:458–64.

[10] Kim S, Jain M, Harris AB, et al. T1 hyperintense renal lesions: characterization with diffusion-weighted MR imaging versus contrast-enhanced MR imaging. Radiology 2009;251:796–807.

[11] Sandrasegaran K, Sundaram CP, Ramaswamy R, et al. Usefulness of diffusion-weighted imaging in the evaluation of renal masses. AJR Am J Roentgenol 2010;194:438–45.

[12] Taouli B, Thakur RK, Mannelli L, et al. Renal lesions: characterization with diffusion-weighted imaging versus contrast-enhanced MR imaging. Radiology 2009;251:398–407.

[13] Ficarra V, Brunelli M, Cheng L, et al. Prognostic and therapeutic impact of the histopathologic definition of parenchymal epithelial renal tumors. Eur Urol 2010;58:655–68.

[14] Wang H, Cheng L, Zhang X, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. Radiology 2010;257:135–43.

[15] Paudyal B, Paudyal P, Tsushima Y, et al. The role of the ADC value in the characterisation of renal carcinoma by diffusion-weighted MRI. Br J Radiol 2010;83:336–43.

[16] Yoshikawa T, Kawamitsu H, Mitchell DG, et al. ADC measurement of abdominal organs and lesions using parallel imaging technique. AJR Am J Roentgenol 2006;187:1521–30.

[17] Manenti G, Di Roma M, Mancino S, et al. Malignant renal neoplasms: correlation between ADC values and cellularity in diffusion weighted magnetic resonance imaging at 3 T. Radiol Med 2008;113:199–213.

[18] Kilickesmez O, Inci E, Atilla S, et al. Diffusion-weighted imaging of the renal and adrenal lesions. J Comput Assist Tomogr 2009;33: 828–33.

[19] Rosenkrantz AB, Niver BE, Fitzgerald EF, Babb JS, Chandarana H, Melamed J. Utility of the apparent diffusion coefficient for distinguishing clear cell renal cell carcinoma of low and high nuclear grade. AJR Am J Roentgenol 2010;195:W344–51.

[20] Doğanay S, Kocakoç E, Ciçekçi M, Ağlamiş S, Akpolat N, Orhan I. Ability and utility of diffusion-weighted MRI with different b values in the evaluation of benign and malignant renal lesions. Clin Radiol 2011;66:420–5.

[21] Razek AA, Farouk A, Mousa A, Nabil N. Role of diffusion-weighted magnetic resonance imaging in characterization of renal tumors. J Comput Assist Tomogr 2011;35:332–6.

[22] Inci E, Hocaoglu E, Aydin S, Cimilli T. Diffusion-weighted magnetic resonance imaging in evaluation of primary solid and cystic renal masses using the Bosniak classification. Eur J Radiol. In press.

[23] Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61–71.

[24] Miao H, Fukatsu H, Ishigaki T. Prostate cancer detection with 3-T MRI: comparison of diffusion-weighted and T2-weighted imaging. Eur J Radiol 2007;61:297–302.

[25] Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. J Magn Reson Imaging 2007;25:146–52.

[26] Haider MA, van der Kwast TH, Tanguay J, et al. Combined T2-weighted and diffusion-weighted MRI for localization of prostate cancer. AJR Am J Roentgenol 2007;189:323–8.

[27] Lim HK, Kim JK, Kim KA, Cho KS. Prostate cancer: apparent diffusion coefficient map with T2-weighted images for detection—a multireader study. Radiology 2009;250:145–51.

[28] Yoshimitsu K, Kiyoshima K, Irie H, et al. Usefulness of apparent diffusion coefficient map in diagnosing prostate carcinoma: correlation with stepwise histopathology. J Magn Reson Imaging 2008; 27:132–9.

[29] Kajihara H, Hayashida Y, Murakami R, et al. Usefulness of diffusion-weighted imaging in the localization of prostate cancer. Int J Radiat Oncol Biol Phys 2009;74:399–403.

[30] Mazaheri Y, Hricak H, Fine SW, et al. Prostate tumor volume measurement with combined T2-weighted imaging and diffusion-weighted MR: correlation with pathologic tumor volume. Radiology 2009;252:449–57.

[31] Gibbs P, Pickles MD, Turnbull LW. Diffusion imaging of the prostate at 3.0 Tesla. Invest Radiol 2006;41:185–8.

[32] Tamada T, Sone T, Jo Y, et al. Apparent diffusion coefficient values in peripheral and transition zones of the prostate: comparison between normal and malignant prostatic tissues and correlation with histologic grade. J Magn Reson Imaging 2008;28:720–6.

[33] Pickles MD, Gibbs P, Sreenivas M, Turnbull LW. Diffusion-weighted imaging of normal and malignant prostate tissue at 3.0T. J Magn Reson Imaging 2006;23:130–4.

[34] Kim CK, Park BK, Han JJ, Kang TW, Lee HM. Diffusion-weighted imaging of the prostate at 3 T for differentiation of malignant and benign tissue in transition and peripheral zones: preliminary results. J Comput Assist Tomogr 2007;31:449–54.

[35] Manenti G, Squillaci E, Di Roma M, Carlani M, Mancino S, Simonetti G. In vivo measurement of the apparent diffusion coefficient in normal and malignant prostatic tissue using thin-slice echo-planar imaging. Radiol Med 2006;111:1124–33.

[36] Sato C, Naganawa S, Nakamura T, et al. Differentiation of noncancerous tissue and cancer lesions by apparent diffusion coefficient values in transition and peripheral zones of the prostate. J Magn Reson Imaging 2005;21:258–62.

[37] Reinsberg SA, Payne GS, Riches SF, et al. Combined use of diffusion-weighted MRI and 1H MR spectroscopy to increase accuracy in prostate cancer detection. AJR Am J Roentgenol 2007;188:91–8.

[38] Kumar V, Jagannathan NR, Kumar R, et al. Apparent diffusion coefficient of the prostate in men prior to biopsy: determination of a cut-off value to predict malignancy of the peripheral zone. NMR Biomed 2007;20:505–11.

[39] deSouza NM, Reinsberg SA, Scurr ED, Brewster JM, Payne GS. Magnetic resonance imaging in prostate cancer: the value of apparent diffusion coefficients for identifying malignant nodules. Br J Radiol 2007;80:90–5.

[40] Kim JH, Kim JK, Park BW, Kim N, Cho KS. Apparent diffusion coefficient: prostate cancer versus noncancerous tissue according to anatomical region. J Magn Reson Imaging 2008;28:1173–9.

[41] Kitajima K, Kaji Y, Kuroda K, Sogimura K. High b-value diffusion-weighted imaging in normal and malignant peripheral zone tissue of the prostate: effect of signal-to-noise ratio. Magn Reson Med Sci 2008;7:93–9.

[42] Zelhof B, Pickles M, Liney G, et al. Correlation of diffusion-weighted magnetic resonance data with cellularity in prostate cancer. BJU Int 2009;103:883–8.

[43] Gibbs P, Liney GP, Pickles MD, Zelhof B, Rodrigues G, Turnbull LW. Correlation of ADC and T2 measurements with cell density in prostate cancer at 3.0 Tesla. Invest Radiol 2009;44:572–6.

[44] Wang XZ, Wang B, Gao ZQ, et al. Diffusion-weighted imaging of prostate cancer: correlation between apparent diffusion coefficient values and tumor proliferation. J Magn Reson Imaging 2009;29: 1360–6.

[45] Woodfield CA, Tung GA, Grand DJ, Pezzullo JA, Machan JT, Renzulli II JF. Diffusion-weighted MRI of peripheral zone prostate cancer: comparison of tumor apparent diffusion coefficient with Gleason score and percentage of tumor on core biopsy. AJR Am J Roentgenol 2010;194:W316–22.

[46] Kim CK, Park BK, Kim B. High-b-value diffusion-weighted imaging at 3 T to detect prostate cancer: comparisons between b values of 1,000 and 2,000 s/mm^2. AJR Am J Roentgenol 2010; 194:W33–7.

[47] Oto A, Kayhan A, Jiang Y, et al. Prostate cancer: differentiation of central gland cancer from benign prostatic hyperplasia by using diffusion-weighted and dynamic contrast-enhanced MR imaging. Radiology 2010;257:715–23.

[48] Langer DL, van der Kwast TH, Evans AJ, et al. Prostate tissue composition and MR measurements: investigating the relationships between ADC, T2, K(trans), v(e), and corresponding histologic features. Radiology 2010;255:485–94.

[49] Yamamura J, Salomon G, Buchert R, et al. Magnetic resonance imaging of prostate cancer: diffusion-weighted imaging in comparison with sextant biopsy. J Comput Assist Tomogr 2011;35: 223–8.

[50] Park BK, Lee HM, Kim CK, Choi HY, Park JW. Lesion localization in patients with a previous negative transrectal ultrasound biopsy and persistently elevated prostate specific antigen level using diffusion-weighted imaging at three Tesla before rebiopsy. Invest Radiol 2008;43:789–93.

[51] Beyersdorff D, Winkel A, Hamm B, Lenk S, Loening SA, Taupitz M. MR imaging-guided prostate biopsy with a closed MR unit at 1.5 T: initial results. Radiology 2005;234:576–81.

[52] deSouza NM, Riches SF, Vanas NJ, et al. Diffusion-weighted magnetic resonance imaging: a potential non-invasive marker of tumour aggressiveness in localized prostate cancer. Clin Radiol 2008;63:774–82.

[53] Hambrock T, Somford DM, Huisman HJ, et al. Relationship between apparent diffusion coefficients at 3.0-T MR imaging and Gleason grade in peripheral zone prostate cancer. Radiology 2011;259: 453–61.

[54] Turkbey B, Shah VP, Pang Y, et al. Is apparent diffusion coefficient associated with clinical risk scores for prostate cancers that are visible on 3-T MR images? Radiology 2011;258:488–95.

[55] Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. Radiology 2011;259:775–84.

[56] Verma S, Rajech A, Morales H, et al. Assessment of aggressiveness of prostate cancer: correlation of apparent diffusion coefficient with

histologic grade after radical prostatectomy. AJR Am J Roentgenol 2011;196:374–81.

[57] Petralia G, Thoeny HC. DW-MRI of the urogenital tract: applications in oncology. Cancer Imaging 2010;10:S112–23.

[58] Eggener SE, Scardino PT, Walsh PC, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 2011;185:869–75.

[59] Kim CK, Choi D, Park BK, Kwon GY, Lim HK. Diffusion-weighted MR imaging for the evaluation of seminal vesicle invasion in prostate cancer: initial results. J Magn Reson Imaging 2008;28:963–9.

[60] Ren J, Huan Y, Wang H, et al. Seminal vesicle invasion in prostate cancer: prediction with combined T2 weighted and diffusion-weighted MR imaging. Eur Radiol 2009;30:351–6.

[61] van As NJ, de Souza NM, Riches SF, et al. A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. Eur Urol 2009; 56:981–8.

[62] Giles SL, Morgan VA, Riches SF, Thomas K, Parker C, deSouza NM. Apparent diffusion coefficient as a predictive biomarker of prostate cancer progression: value of fast and slow diffusion components. AJR Am J Roentgenol 2011;196:586–91.

[63] Morgan VA, Riches SF, Thomas K, et al. Diffusion-weighted magnetic resonance imaging for monitoring prostate cancer progression in patients managed by active surveillance. Br J Radiol 2011; 84:31–7.

[64] Nishida K, Yuen S, Kamoi K, et al. Incremental value of T2-weighted and diffusion-weighted MRI for prediction of biochemical recurrence after radical prostatectomy in clinically localized prostate cancer. Acta Radiol 2011;52:120–6.

[65] Park SJ, Kim CK, Park BK, Lee HM, Lee KS. Prediction of biochemical recurrence following radical prostatectomy in men with prostate cancer by diffusion-weighted magnetic resonance imaging: initial results. Eur Radiol 2011;21:1111–8.

[66] Martino P, Scattoni V, Galosi AB, et al. Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). World J Urol 2011;29:595–605.

[67] Westphalen AC, Coakley FV, Roach M, McCulloch CE, Kurhanewicz J. Locally recurrent prostate cancer after external beam radiation therapy: diagnostic performance of 1.5-T endorectal MR imaging and MR spectroscopic imaging for detection. Radiology 2010;256: 485–92.

[68] Kim CK, Park BK, Lee HM. Prediction of locally recurrent prostate cancer after radiation therapy: incremental value of 3T diffusion-weighted MRI. J Magn Reson Imaging 2009;29:391–7.

[69] Kim CK, Park BK, Park W, Kim SS. Prostate MR imaging at 3T using a phased-arrayed coil in predicting locally recurrent prostate cancer after radiation therapy: preliminary experience. Abdom Imaging 2010;35:246–52.

[70] Tamada T, Sone T, Jo Y, et al. Locally recurrent prostate cancer after high-dose-rate brachytherapy: the value of diffusion-weighted imaging, dynamic contrast-enhanced MRI, and T2-weighted imaging in localizing tumors. AJR Am J Roentgenol 2011;197:408–14.

[71] Warmuth M, Johansson T, Mad P. Systematic review of the efficacy and safety of high-intensity focussed ultrasound for the primary and salvage treatment of prostate cancer. Eur Urol 2010;58:803–15, Corrigendum. Eur Urol 2011;59:476.

[72] De Visschere PJ, De Meerleer GO, Futterer JJ, Villeirs GM. Role of MRI in follow-up after focal therapy for prostate carcinoma. AJR Am J Roentgenol 2010;194:1427–33.

[73] Kim CK, Park BK, Lee HM, Kim SS, Kim E. MRI techniques for prediction of local tumor progression after high-intensity focused ultrasonic ablation of prostate cancer. AJR Am J Roentgenol 2008;190:1180–6.

[74] Eggener S, Salomon G, Scardino PT, De la Rosette J, Polascik TJ, Brewster S. Focal therapy for prostate cancer: possibilities and limitations. Eur Urol 2010;58:57–64.

[75] Abou-El-Ghar ME, El-Assmy A, Refaie HF, El-Diasty T. Bladder cancer: diagnosis with diffusion-weighted MR imaging in patients with gross hematuria. Radiology 2009;251:415–21.

[76] Ceylan K, Taken K, Gecit L, et al. Comparison of cystoscopy with diffusion-weighted magnetic resonance images used in the diagnosis and follow-up of patients with bladder tumors. Asian Pacific J Cancer Prev 2010;11:1001–4.

[77] Matsuki M, Inada Y, Tatsugami F, Tanikake M, Narabayashi I, Katsuoka Y. Diffusion-weighted MR imaging for urinary bladder carcinoma: initial results. Eur Radiol 2007;17:201–4.

[78] El-Assmy A, Abou-El-Ghar ME, Refaie HF, El-Diasty T. Diffusion-weighted MR imaging in diagnosis of superficial and invasive urinary bladder carcinoma: a preliminary prospective study. Scientific World Journal 2008;8:364–70.

[79] Kiliçkesmez O, Cimilli T, Inci E, et al. Diffusion-weighted MRI of urinary bladder and prostate cancers. Diagn Interv Radiol 2009;15: 104–10.

[80] Avcu S, Akdeniz H, Unal O, Kurdoglu M. The value of diffusion-weighted MRI in the diagnosis of malignant and benign urinary bladder lesions. Br J Radiol 2011;84:875–82.

[81] Stenzl A, Cowan NC, De Santis M, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol 2011;59:1009–18.

[82] Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder, the 2011 update. Eur Urol 2011;59:997–1008.

[83] El-Assmy A, Abou-El-Ghar ME, Mosbah A, et al. Bladder tumour staging: comparison of diffusion- and T2-weighted MR imaging. Eur Radiol 2009;19:1575–81.

[84] Takeuchi M, Sasaki S, Ito M, et al. Urinary bladder cancer: diffusion-weighted MR imaging—accuracy for diagnosing T stage and estimating histologic grade. Radiology 2009;251:112–21.

[85] Watanabe H, Kanematsu M, Kondo H, et al. Preoperative T staging of urinary bladder cancer: does diffusion-weighted MRI have supplementary value? AJR Am J Roentgenol 2009;192:1361–6.

[86] Yoshida S, Koga F, Kawakami S, et al. Initial experience of diffusion-weighted magnetic resonance imaging to assess therapeutic response to induction chemoradiotherapy against muscle-invasive bladder cancer. Urology 2010;75:387–91.

[87] Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55:1251–65.

[88] Karl A, Carroll PR, Gschwend JE, et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. Eur Urol 2009;55:826–35.

[89] McMahon CJ, Rofsky NM, Pedrosa I. Lymphatic metastases from pelvic tumors: anatomic classification, characterization, and staging. Radiology 2010;254:31–46.

[90] Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. J Clin Oncol 2005;23:2358–65.

[91] Schumacher MC, Burkhard FC, Thalmann GN, Fleischmann A, Studer UE. Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. Eur Urol 2008;54: 344–52.

[92] Eiber M, Beer AJ, Holzapfel K, et al. Preliminary results for characterization of pelvic lymph nodes in patients with prostate cancer by diffusion-weighted MR-imaging. Invest Radiol 2010;45:15–23.

[93] Beer AJ, Eiber M, Souvatzoglou M, et al. Restricted water diffusibility as measured by diffusion-weighted MR imaging and choline uptake in (11)C-choline PET/CT are correlated in pelvic lymph

nodes in patients with prostate cancer. Mol Imaging Biol 2011; 13:352–61.

[94] Budiharto T, Joniau S, Lerut E, et al. Prospective evaluation of ^{11}C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. Eur Urol 2011;60:125–30.

[95] Thoeny HC, Triantafyllou M, Birkhaeuser FD, et al. Combined ultrasmall superparamagnetic particles of iron oxide–enhanced and diffusion-weighted magnetic resonance imaging reliably detect pelvic lymph node metastases in normal-sized nodes of bladder and prostate cancer patients. Eur Urol 2009;55:761–9.

[96] Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011;59:477–94.

[97] Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102–25.

[98] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol 2010;58:398–406.

[99] Sciarra A, Barentsz J, Bjartell A, et al. Advances in magnetic resonance imaging: how they are changing the management of prostate cancer. Eur Urol 2011;59:962–77.

Infection/ inflammation

1. **Chyluria**
    - **Chyluria is caused by lymphatic rupture or fistulous connection into the pyelocalyceal system.** It is a rare problem worldwide but is commonly seen in tropical countries where filariasis (*Wuchereria bancrofti* or *Brugia malayi*), the most common cause, is endemic.
    - Rarely, schistosomiasis may also be a cause of chyluria, and nonparasitic chyluria is rare.
    - Other reported causes include tuberculosis, idiopathic lymphorenal fistula, prior surgery, pregnancy, thoracic duct obstruction, mesenteric adenitis, renal vasculitis, and metanephric adenoma.
    - **Diagnosis**
        - Patients typically have milky white urine and may have nephritic range proteinuria
        - Initial evaluation includes urinalysis and culture
        - Urine for chyle, and complete blood count to check for eosinophilia
        - Cystoscopy to localize the fistula side
        - Other localization investigations include: retrograde pyelogram, IVU, CT, MRI, or lymphangiography
    - **Treatment**
        - Chyluria is often self-limited, and many patients may be managed conservatively
        - Low-fat diet with medium chain fatty acids is advised
        - Diethylcarbamazine (DEC) is effective in filariasis-associated chyluria
        - Retrograde instillation of silver nitrate or povidone iodine into the collecting system as a sclerosing agent has also been described, and these agents are commonly used as first-line treatment with comparable success rates of approximately 80%.
        - When conservative management fails or if cases are particularly severe, surgical intervention is undertaken. This includes pyelolymphatic disconnection or nephrolysis which can be performed laparoscopicaly. Nephrolysis involves the complete mobilization of the kidney and skeletonization of the renal hilar vessels and upper ureter with ligation of the lymphatic channels. The use of an omental wrap around the hilum has also been described to reduce recurrence.
        - For recurrent and severe cases even after pyelolymphatic disconnection, autotransplantation of the affected renal unit is an option.

2. **Schistosomiasis**
    - **Causative organisms:** 3 species of primary medical importance are
        - *Schistosoma mansoni* (Africa, Arabian Peninsula, and South America)
        - *Schistosoma japonicum* (China and Southeast Asia)
        - *Schistosoma haematobium* (Africa and the Arabian Peninsula)
    - *S. mansoni* and *S. japonicum* primarily affect the liver and GI tract, *S. haematobium* infection primarily affects the GU tract.
    - German pathologist Theodor Bilharz, performing autopsies in Cairo in 1852, found worms in mesenteric veins and linked them to eggs found in human urine and stool.
    - **Biology and life cycle**
        - Human infection is initiated by the penetration of *S. haematobium* cercariae through skin (even intact) from infested fresh water
        - Average life span of cercariae is 1 day
        - After penetration, cercariae transform into an obligate parasites called *schistosomulae* within 2 hours
        - Schistosomulae migrate to **lungs** via bloodstream or lymphatics, and then liver via the venous circulation. This takes several weeks.
        - In liver sinusoids *schistosomes* begin blood feeding and get matured
        - Mature worms preferentially migrate to the venous plexus of the bladder and other pelvic organs, where they live an average of 3 to 5 years.
        - Developmental period from cercaria to adult worm ranges from 80 to 110 days.
        - Eggs are laid by adult female worms in the pelvic venous circulation (hundreds to thousands of eggs per female per day). *S. haematobium* eggs are ovoid and have a terminal spine.
        - Eggs penetrate the endothelium to reach the lumen of bladder to exit via the urinary stream, reach fresh water, and hatch into larvae which infect intermediate host snails.
    - **Pathology**
        - Main immunopathologic responses against *S. haematobium* are triggered by oviposition in the walls of the bladder and other pelvic organs.
        - Eggs lead to granuloma development and eventual fibrosis, often obstructing the flow of blood or urine. Granulomas are characterized by a mixed leukocytic infiltration, including eosinophils, plasma cells, and lymphocytes. Grossly, granulomatous inflammation can form bulky, hyperemic, and polypoid masses projecting into the bladder lumen.
        - Retained eggs get calcified and results in decreased compliance of urinary tract and increases upper tract pressures, and hydronephrosis, and hydroureter.
        - Long-term infection may cause urothelial hyperplasia, squamous metaplasia, urothelial dysplasia, and eventually urothelial or Squamous cell carcinoma. Bladder cancer is the final pathologic sequela of schistosomiasis.

  - Schistosomal bladder cancer
    - Early onset (40 to 50 years)
    - Squamous cell carcinoma (60% to 90%) or adenocarcinoma (5% to 15%)
    - 40% of these SCC are well differentiated and verrucous and have overall good prognosis.

- **Clinical Manifestations**
  - **Acute Schistosomiasis**
    - The first clinical manifestation of schistosomiasis is often an itchy maculopapular rash (cercarial dermatitis), usually within 1 to 2 days of cercarial penetration.
    - Katayama fever: is the syndrome of acute schistosomiasis seen in Katayama Valley in Japan, which occurs with heavy primary infections. Initial signs and symptoms include fever, dry cough, fatigue, headache, diarrhea, eosinophilia, neck pain, and urticaria.
  - **Chronic Schistosomiasis**
    - Egg shedding by adult worms is heralded by painless, recurrent gross hematuria, dysuria, or urinary frequency.
    - Fibrosis may obstruct urinary drainage and result in organ dysfunction.
    - Egg deposition in the ureters and subsequent granuloma, polyp, and ulcer formation increases the risk of hydronephrosis and hydroureter caused by impaired peristalsis of the walls of the renal pelvis and ureter, which in turn can result in obstruction, and VUR.
    - In late, chronic, active stage chronic suprapubic and pelvic pain with urgency, frequency, and incontinence are classic features of schistosomal contracted bladder. Functional bladder capacity can be as low as 50 mL in adults.

- **Diagnosis**
  - Finding *S. haematobium* eggs in urine or stool remains the gold standard for diagnosis of active infection, although eggs do not appear until oviposition begins 8 to 12 weeks after infection.
  - If eggs are not found in the urine or stool but clinical suspicion remains high and serology is consistent with exposure, a rectal snip biopsy should be performed before a bladder biopsy, because eggs are common in the rectal mucosa and the risk of a bladder biopsy–related complication (e.g. infection, perforation) is avoided.
  - A squash preparation of the biopsy specimen between glass slides is superior to HPE.
  - Serologic tests that combine a FAST-ELISA with a Western blot analysis are available, and are more than 90% sensitive and specific. But it does not distinguish between acute and chronic infection.
  - USG may demonstrate bladder or ureteral wall thickening, polypoid lesions, hydroureter, hydronephrosis, urinary tract calcifications, and even bladder tumor.
  - Plain abdominal radiographs may reveal urinary tract calcifications; a calcified bladder, which may resemble a fetal head in the pelvis, is characteristic of chronic urogenital schistosomiasis
  - IVU: shows striations in the ureters and renal pelvis. Ureteral calcification is typically intra-mural and the ureters are dilated. This differs from the calcifications seen in TB, which form casts of nondilated ureters. Other findings on IVU include HDN, HUN, non-functioning kidney, ureteral stenosis, and bladder and ureteral filling defects caused by polypoid lesions.
  - CT can detect both obstructive uropathy and calcified lesions in the colon and urinary tract

- **Treatment**
  - **Medical Management**
    - Praziquantel (PZQ) is currently the only WHO-recommended drug for schistosomiasis. Two 20-mg/kg oral doses of PZQ are given on the same day, 6 to 8 hours apart (or alternatively, one 40- or 60-mg/kg dose). PZQ's efficacy is 60% to 90% and is more effective against adult worm.
    - Corticosteroids are often added for the treatment of acute schistosomiasis (Katayama fever).
    - Artemisinin and its analogues (artemether and artesunate) are alternatives to PZQ because they specifically target the schistosomule stage.They *a*re 90% to 97% efficacious for prevention.
  - **Surgical Management**
    - Surgery is reserved for complications that have not responded to medical treatment and for those settings in which immediate surgical intervention is necessary e.g. severe hematuria.
    - Surgery is always combined with medical chemotherapy.
    - Surgery is indicated for irreversibly contracted bladders; procedures include vesical denervation, urinary diversion, ileocystoplasty, and hydrodistention. Chronic, deep bladder ulcers may need partial cystectomy, because fulguration is rarely effective.
    - Surgery is also typically required for bladder cancer secondary to schistosomiasis.
    - Medical management can prevent and reverses schistosomal obstructive uropathy of acute and active stage of disease. Late and chronic stages obstruction may need drainage of upper tracts.
    - Residual ureteral stenosis after chemotherapy is treated by balloon dilatation or excision depending on location.

3. Bacterial biofilm

- Biofilm formation- most common cause of stent or urinary prosthesis failure
- Definition→ an attempt of micro-organisms to control their micro-environment by limiting exposure to harmful factors & enhancing exposure to trophic factors
- Bacteria residing in biofilm can undergo **metabolic dormancy**, which may lead to increased **antibiotic resistance**. They can also **communicate** with each other to start dispersal & detachment. In this way, biofilm structure & bacteria residing within it behave **like a tissue of a higher organism.**
- Size (thickness) of biofilm ranges from few isolated monolayers to 400 cells deep, reaching a population of up to 5×10^9 CFU
- **Structure of biofilm→ 3 layers**
    i. Innermost layer/ Linking film→ attached to the surface of biomaterial
    ii. Base film→ contains micro-organisms
    iii. Outermost layer/ Surface film→ point of access/egress
- **Steps in the development of biofilm**
    i. **Formation of 'Conditioning layer'**
        - Deposition of urinary constituents (proteins, electrolytes) on biomaterial surface
        - Occurs within few minutes of insertion of stent/catheter
        - Modifies the biomaterial surface by blocking or providing receptors sites
    ii. **Bacterial adhesion**
        - Influenced by multiple factors including- electrostatic & hydrostatic interactions, ionic forces, osmolality & pH of urine
    iii. **Cell division**
        - Organisms divide and form microcolonies inside the matrix of bacterial exo-polysaccharides & glycocalix
        - At this stage, eradication of biofilm is NOT possible, and removal of biomaterial becomes essential for treatment
- Biofilm formation may be the preliminary step for encrustation especially when infection with urease producers (increased urine pH leading to precipitation of Ca^{2+} & Mg^{2+} salts). [Acidic urinary pH increases the solubility of Ca^{2+}]
- **Clinical significance:**
    - Results in bacterial persistence
    - Increased antibiotic resistance
    - Biomaterial needs to be removed completely for treatment

4. GUTB- Pathophysiology, manifestations and management in adult male (essay)

Tuberculosis is caused by a group of closely related acid-fast bacteria referred to as the *Mycobacterium tuberculosis* complex (MTBC). The most frequently isolated species in human TB is *M. tuberculosis.*
One third of the world's population is infected with MTBC in its latent form.

- **Pathophysiology**
    - Initial mode of entry of MTBC into the host is via inhalation. After reaching the alveoli in the lungs, they are phagocytosed by alveolar macrophages. If MTBC are killed by macrophages at this point and effectively cleared from the body, infection or an adaptive immunity does not occur. In others individuals, MTBC bacilli escape killing, begin to replicate within macrophages, and establish infection. A cellular immune response can be detected in up to 12 weeks. Before the development of cellular immunity, tubercle bacilli can spread through the lymphatics to lymph nodes and through bloodstream to distant organs.
    - GU TB has been found in 2% to 10% of patients with pulmonary TB in developed countries. In contrast, the frequency in developing countries (India) approaches 15% to 20%.
    - Host attempts to contain MTBC infection by forming granulomas. Foamy macrophages, epithelioid cells, and multinucleated giant cells (Langhans cells) cluster to the center and surrounded by a cuff of lymphocytes constitute granuloma. All these immune cells are recruited by inflammatory cytokines (IL-6, IL-12, IL-1β, and TNF-α) which are secreted by the infected macrophages.
    - Immune cells of granuloma process and present antigens to T-cells leading to T-cell activation. This results in an adaptive cellular response against MTBC. T-cells secrete cytokines such as IL-2, TNF-α, and IFN-γ to induce killing of infected macrophages and the bacilli. Even if killing is not achieved, the granuloma can still successfully sequester viable bacilli in non-replicating and dormant phase. In 90% to 95% of persons, TB is controlled at this point and enters latency, which is marked by cicatrization and granuloma **calcifcation**.
    - In <5% of infected persons, the initial infection progresses within a year to active TB (primary progression). Dormant bacilli from latent TB can also become active years later to cause active TB (secondary progression). Risk factors for reactivation are old age, renal failure, diabetes mellitus, malnutrition, HIV infection, and immune suppression of any cause. Lifetime risk of reactivation TB is 5% to 10%.

  - **Development of GUTB:** There are 4 means by which GU TB develops
    1. Hematogenous: Principal route of spread to GU system. Typical sites for GU seeding are kidneys and epididymis (The first and the second most common organs involved in GU system)
    2. Ascending or retrograde spread: 2nd most common route of infection. E.g. GUTB after bladder irrigation with BCG for the treatment of bladder cancer.
    3. Contiguous or direct inoculation: rare. Spread to GU system from other organ systems. E.g. Extension of TB from the spine and psoas to the kidneys.
    4. Other routes: Lymphatic spread, genital inoculation after contact with infected genital, stool or urine or oral lesions.
    5. Involvement of GU organs other than kidney and epididymis is usually by secondary spread

- **Clinical manifestations**
  - Symptoms and signs of GUTB are often non-specifc. Patients are often treated for other bacterial infections (sometimes repeatedly) or are evaluated for possible malignancy before GUTB is considered. Symptoms depend on the location of disease. Renal TB can be progressive and destructive but symptomatically silent until it extends into the bladder.
  - Typical TB constitutional symptoms of fever, weight loss, night sweats, and malaise are present in fewer than 20% of patients.
  - Up to 50% of patients with GUTB have only dysuria on presentation, 50% have storage symptoms, and 33% have hematuria and flank pain. Renal colic occurs in < 10%, and is due to passage of sloughed necrotic papillae, clots, stones, and caseous phlegmon.
  - Typical laboratory findings include sterile pyuria and/or hematuria. This combination is found in more than 90% cases of GUTB.
  - Epididymal and vas involvement causes hard nodular epididymis and thickened vas with obliterated lumen. Patient may present with scrotal mass, discharging sinus or infertility.
  - Prostate TB results in abscess formation in immunocompromised patients. It can be silent involvement found as nodular prostate.

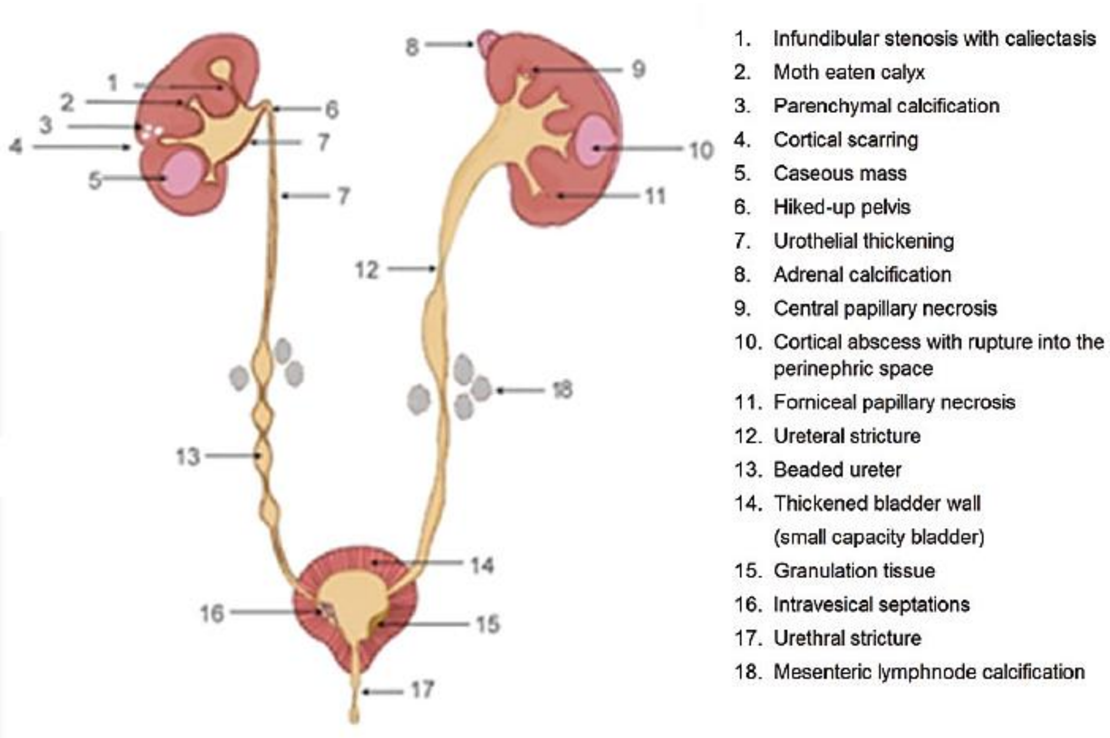
- **Diagnosis**
  - **Microbiological diagnosis**
    1. **Urine AFB smear (By Acid-fast or ZN staining)**
       - At least 3 (preferably 5) early morning urine samples should be analysed.
       - In case of increased day/night frequency, at least 8 hours of collection of urine is required. Sterile containers with specific inhibitors required for collection of samples.
       - A bacterial load of 5000 organisms/ml is needed for positive smear.
       - This staining is based on the presence of large amounts of lipid substances within their cell walls called mycolic acids which resist ordinary staining such as Gram staining. Acid fast bacilli appear bright red on ZN staining.
       - Sensitivity and specifcity of 60-70% and 90-95% respectively.
       - Auramine/Rhodamine (AR) staining with fluorescent microscopy increases sensitivity by 10-15% as compared to ZN staining.
    2. **Culture**
       - Three types of culture media are used→ Egg based (LJ), Agar based (Middlebrook 7H10 or 7H11), and Liquid based (Middlebrook 7H9).
       - AFB culture by conventional LJ medium is the gold standard and has a sensitivity and specificity of 80-85% and 98% respectively. Main drawback is that it takes 6-8 weeks for the results.
       - Radiometric (radionuclear material based) culture methods give results in 2-3 wks and are equally sensitive (now replaced by MGIT, because of involved risk of radiation).
       - Mycobacterial Growth Indicator Tube (MGIT) uses Middlebrook 7H9 broth (liquid) with oxygen sensitive fluorescent sensor at bottom. Positive results are obtained in 10-12 days.
    3. **Immunologic Assays (Screening tests)**
       - **Mantoux skin test (PPD):** Its role in Indian population is questionable. Problems with PPD are administering, interpretation in already immunized persons with BCG, need of second visit for interpretation and lower specificity in developing countries where prevalence of TB is higher.
       - **IFN-γ release assays (IGRAs):** These are in-vitro blood tests that measure the level of IFN-γ (a surrogate of cellular immune reactivity) produced in response to MTBC-specific antigens. These specific antigens are not present in the BCG vaccine, but false-positive results can be caused by previous environmental exposure mycobacteria. The IFN-γ release assay has a sensitivity of 84-95% and a specifcity of 85-99%. Results are available after 24 hours. **QuantiFERON**-TB Gold In-Tube test (QFT-GIT) is a type of IGRA test.

iv. **Molecular techniques**

- **NAAT- PCR (Nucleic Acid Amplification Tests)** methods have sensitivity of 70-100% and specificity of 80-100%. PCR assays may target either DNA or rRNA. It can also detect drug resistance. NAATs provide results rapidly within 1-2 days. Issue are cost and the fact that unlike cultures, NAATs cannot be used to monitor treatment response because it can not differentiate between line and dead organisms.
- **GeneXpert MTB/RIF** is fully-automated NAAT based test that detects tubercular resistance to rifampicin. It has demonstrated 100% sensitivity on urine samples. This assay is a self-contained Cartridge-based (CBNAAT) test, does not require intensive training to use, can give a result in less than 2 hours and was shown to correctly identify 97.6% of rifampicin-resistant bacilli in sputum.

v. **Radiological studies**

- **Plain X-ray KUB, USG, IVU, CT urography, and MRI** all have their role. However, best diagnostic imaging is provided by the IVU and CT scan, IVU now being replaced by CT urography.
- **Important imaging features on IVU include**: Moth-eaten or fuzzy appearance f calyces, calyceal obliteration, infundibular stenosis, hydrocalycosis, segmental or total hydronephrosis, phantom calyx, contracted and/or hiked-up renal pelvis, with sharp angulation of UPJ (Kerr's kink), medullary cavities that communicate with PCS, renal calcification, non-visualized kidney, hydroureter, rigid, calcifed, straightened, pipestem ureter or sometimes corkscrew ureter, VUJ strictures, VUR, and small capacity contracted bladder.
- CT scan has additional role in detecting perinephric extensions and abscesses, providing surgical anatomy and surrounding relations.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1. Infundibular stenosis with caliectasis
2. Moth eaten calyx
3. Parenchymal calcification
4. Cortical scarring
5. Caseous mass
6. Hiked-up pelvis
7. Urothelial thickening
8. Adrenal calcification
9. Central papillary necrosis
10. Cortical abscess with rupture into the perinephric space
11. Forniceal papillary necrosis
12. Ureteral stricture
13. Beaded ureter
14. Thickened bladder wall (small capacity bladder)
15. Granulation tissue
16. Intravesical septations
17. Urethral stricture
18. Mesenteric lymphnode calcification

- RGP: Currently recommended to assess ureteral stricture length, and to obtain isolated samples of urine from the kidney.

vi. **Cystoscopy and biopsy**

- Should be performed under GA (with muscle relaxants) in a gentle manner. Bladder biopsy is indicated in presence of tubercles or ulcers and should be avoided in acute cystitis phase.

- **Criteria for definitive diagnosis:** One major and/or two minor criteria

Major Criteria	Minor Criteria
1. Granulomatous lesion in biopsy specimen 2. AFB in urine or tissue (smear or culture) 3. Positive PCR	**1.** Imaging findings (IVU/CT/MRI) suggestive of GUTB **2.** Hematuria **3.** Raised ESR **4.** CXR changes of old Kochs

- **Medical treatment**
  - First chance is the best to cure the disease (100%) and in preventing the emergence of resistance. Treatment of MDR-TB is 100 times more expensive and often highly toxic.
  - Short course chemotherapy for 6 months is sufficient which includes 2 months of initial intense treatment phase with 4 drugs followed by 4 months of continuation treatment phase with 2 drugs.

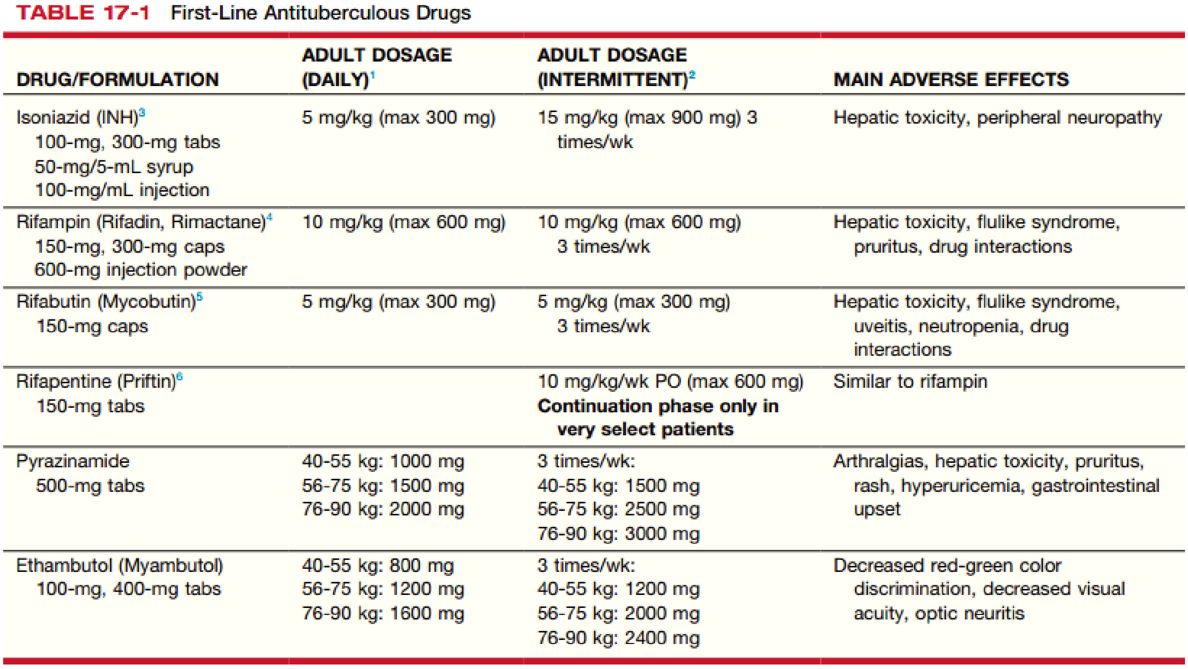


TABLE 17-1 First-Line Antituberculous Drugs

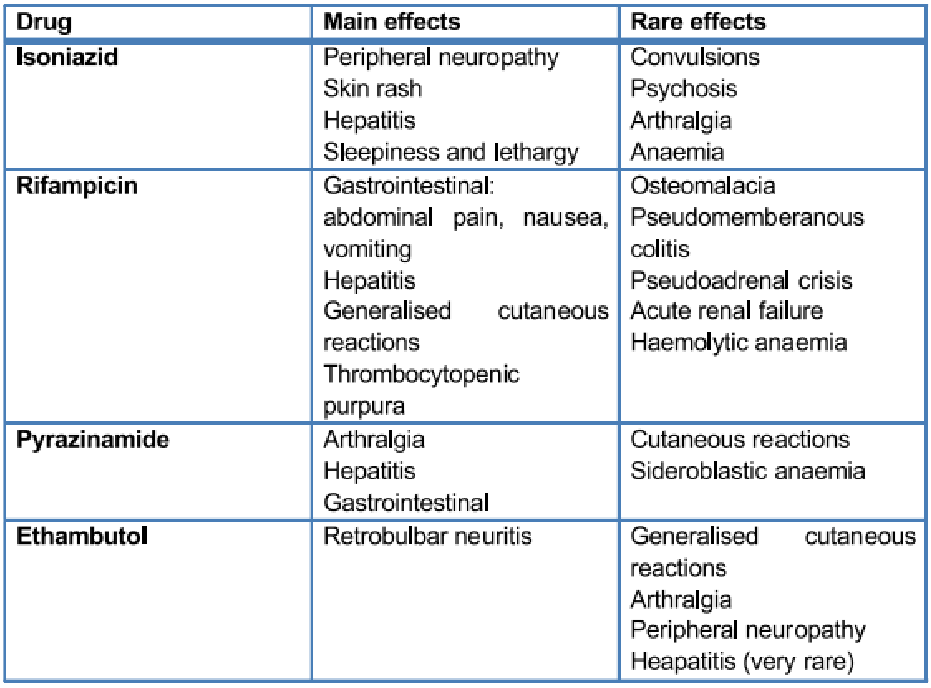
DRUG/FORMULATION	ADULT DOSAGE (DAILY)[1]	ADULT DOSAGE (INTERMITTENT)[2]	MAIN ADVERSE EFFECTS
Isoniazid (INH)[3] 100-mg, 300-mg tabs 50-mg/5-mL syrup 100-mg/mL injection	5 mg/kg (max 300 mg)	15 mg/kg (max 900 mg) 3 times/wk	Hepatic toxicity, peripheral neuropathy
Rifampin (Rifadin, Rimactane)[4] 150-mg, 300-mg caps 600-mg injection powder	10 mg/kg (max 600 mg)	10 mg/kg (max 600 mg) 3 times/wk	Hepatic toxicity, flulike syndrome, pruritus, drug interactions
Rifabutin (Mycobutin)[5] 150-mg caps	5 mg/kg (max 300 mg)	5 mg/kg (max 300 mg) 3 times/wk	Hepatic toxicity, flulike syndrome, uveitis, neutropenia, drug interactions
Rifapentine (Priftin)[6] 150-mg tabs		10 mg/kg/wk PO (max 600 mg) **Continuation phase only in very select patients**	Similar to rifampin
Pyrazinamide 500-mg tabs	40-55 kg: 1000 mg 56-75 kg: 1500 mg 76-90 kg: 2000 mg	3 times/wk: 40-55 kg: 1500 mg 56-75 kg: 2500 mg 76-90 kg: 3000 mg	Arthralgias, hepatic toxicity, pruritus, rash, hyperuricemia, gastrointestinal upset
Ethambutol (Myambutol) 100-mg, 400-mg tabs	40-55 kg: 800 mg 56-75 kg: 1200 mg 76-90 kg: 1600 mg	3 times/wk: 40-55 kg: 1200 mg 56-75 kg: 2000 mg 76-90 kg: 2400 mg	Decreased red-green color discrimination, decreased visual acuity, optic neuritis

  - Second line drugs: Streptomycin, amikacin, capreomycin kanamycin, Cycloserine, Ethionamide, Levofloxacin, Moxifloxacin, Aminosalicylic acid (PAS), Linezolid, and Bedaquiline
  - In cases where isoniazid or rifampin cannot be used, treatment is continued for 12-18 months. If second line treatment is to be offered, treatment is recommended for 18-24 months.
  - ATT is to be taken on empty stomach since food, antacids containing aluminum and magnesium and prokinetics reduces the absorption of the medicines significantly.
  - Streptomycin to be avoided in pregnancy, and Ethambutol in children and in renal failure.
  - **Indications for prolonged therapy**
    - Immunocompromised patient
    - Coexistent HIV/AIDS
  - **Follow up on ATT**
    - Follow up is required to monitor side effects of ATT, development of complications, and also to ensure the compliance with ATT. Monitoring for hepatic toxicity, drug interactions and visual and auditory complications is required.
    - Blood test for LFT, Hb, platelet count, ESR, RFT, serum electrolytes and calcium is done at 1, 2, 4 and 6 months and then as appropriate.
    - Since healing is a prolonged process, ongoing fibrotic changes may lead to mechanical complications like infundibular and ureteral strictures, reducing bladder capacity etc. Therefore, USG, IVU, RGU, cystoscopy and RGP, nephrostograms and radionuclide renal scans may be obtained as appropriate till the structural abnormalities are stabilized.
- **Surgical treatment**
  - Stenting
    - Indications for Stenting: Maintain drainage during medical therapy, and after dilatation of ureteral strictures.
    - Stents are retained if inserted sufficiently long to stabilize strictures which may take a year or two or more. RGP may be obtained without or with ureteroscopy to know progression of stricture. If not resolving, appropriate surgical intervention may be considered.
    - If stent is decided to be removed, follow up may be done with USG, IVU or DTPA/MAG3 in 1-3 months to ensure that restructuring is not developing.
  - PCN
    - Indicated if stent cannot be placed in ureteral strictures, and in infundibular stenosis with calyceal dilatation
  - Nephrectomy
    - Indications: Non-functioning kidney with or without calcification, extensive disease involving whole kidney, HTN due to TB-nephropathy, Co-existing malignancy
    - Nearly 50% of the tuberculous nephrectomy specimens harbour active TB in spite of adequate chemotherapy. Nephrectomy should be planned after at least 4-6 weeks after completion of ATT
  - Partial Nephrectomy

        - Indicated for localised polar lesion with calcification, not responding to 6 weeks of ATT, and area of calcification gradually increasing in size.
    - Reconstruction in GUTB
        - Uretero-vesical junction strictures may require ureteral reimplantation if strictures fail to resolve with ATT and DJ stenting. PUJ strictures may need pyeloplasty in cases not responding to conservative measures like stenting and dilatation. Long stricture of ureter may need ileal ureter replacement.
        - Bladder reconstruction by augmentation cystoplasty is required for very small capacity thickened bladder with severe symptoms.
    - Surgical management is also needed for perinephric or renal abscess (PCD), epididymal abscess not responding to ATT etc.

5. **RNTCP- Categories, regimes, dosage and side-effects of first line drugs**

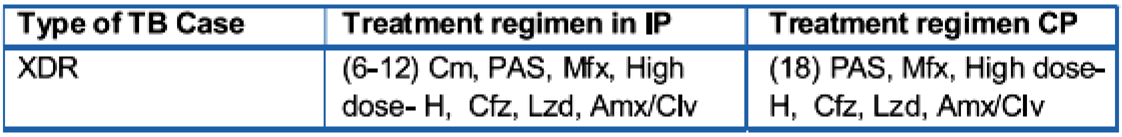
- **RNTCP- Categories**
- **Definitions**
    - Mono resistance (MR) – resistant to one first-line anti-TB drug only
    - Poly resistance (PDR) –resistant to more than one first-line anti-TB drug, other than both INH and Rifampicin
    - Multi-drug resistance (MDR) –resistant to both INH and Rifampicin with or without resistance other first-line drugs
    - Rifampicin resistance (RR) – resistant to Rifampicin with or without resistant to other drugs excluding INH (should be managed as MDR TB)
    - Extensive drug resistance (XDR) – MDR TB case (resistant to INH and Rifampin) and resistant to a FQs and to at least one of the main three SLIDs [Second-line injectable drugs (amikacin, capreomycin or kanamycin)]
- For new cases→ Short course chemotherapy for 6 months is sufficient which includes 2 months of initial intense treatment phase with 4 drugs followed by 4 months of continuation treatment phase with 2 drugs.
- All “relapses, treatment after default, previously-treated, failures and others” are treated with 3 months of initial intense treatment phase with 4 drugs (H,R,Z,E) followed by 5 months of continuation treatment phase with 3 drugs (H,R,E).
- In cases where INH or RIF cannot be used, treatment is continued for 12-18 months. If second line treatment is to be offered, treatment is recommended for 18-24 months.
- Under DOTS administration is 5 times/wkpy (DOT).
  2. Intermittent therapy (administered by DOT) only during the continuation phase of therapy. The World Health Organization (WHO) no longer recommends dosage intervals less frequent than 3 times/wk ATT is to be taken on empty stomach since food, antacids containing aluminum and magnesium and prokinetics reduces the absorption of the medicines significantly.
- Streptomycin to be avoided in pregnancy, and Ethambutol in children and in renal failure.
- **Indications for prolonged therapy**
    - Immunocompromised patient
    - Coexistent HIV/AIDS
- **Regimes, dosage and side-effects of first line drugs→ See the table in Question: 4, and the following table**



Drug	Main effects	Rare effects
Isoniazid	Peripheral neuropathy Skin rash Hepatitis Sleepiness and lethargy	Convulsions Psychosis Arthralgia Anaemia
Rifampicin	Gastrointestinal: abdominal pain, nausea, vomiting Hepatitis Generalised cutaneous reactions Thrombocytopenic purpura	Osteomalacia Pseudomemberanous colitis Pseudoadrenal crisis Acute renal failure Haemolytic anaemia
Pyrazinamide	Arthralgia Hepatitis Gastrointestinal	Cutaneous reactions Sideroblastic anaemia
Ethambutol	Retrobulbar neuritis	Generalised cutaneous reactions Arthralgia Peripheral neuropathy Heapatitis (very rare)

6. XDR TB

- **Definition of XDR TB**
    - Extensive drug resistance (XDR) – MDR TB case (resistant to INH and Rifampin) and resistant to a FQs and to at least one of the main three SLIDs [Second-line injectable drugs (amikacin, capreomycin or kanamycin)]
- **Risk factors for XDR TB**
    - Inadequate primary treatment
    - Incomplete treatment or defaulted treatment
    - Treatment with resistant drugs
    - Immunocompromised status
- All XDR-TB patients should be subject to a repeat full pre-treatment evaluation, but also including consultation by a thoracic surgeon for consideration of surgery.
- **Treatment**
    - All drugs should be given in a single daily dosage under supervision.
    - Pyridoxine should be administered to all patients of on the regimen for XDR-TB.
    - Intensive phase: Consist of 7 drugs
        - Capreomycin (Cm), PAS, Moxifloxacin (Mfx), High-dose INH, Clofazimine (Cfz), Linezolid (Lzd), and Amoxiclav (Amx/Clv).
    - Continuation phase: Consist of 6 drugs
        - PAS, Moxifloxacin (Mfx), High-dose INH, Clofazimine (Cfz), Linezolid (Lzd), and Amoxiclav (Amx/Clv).



Type of TB Case	Treatment regimen in IP	Treatment regimen CP
XDR	(6-12) Cm, PAS, Mfx, High dose- H, Cfz, Lzd, Amx/Clv	(18) PAS, Mfx, High dose- H, Cfz, Lzd, Amx/Clv

-
    - Dosage of the drugs would vary as per the weight of the patient.
    - Duration of treatment for XDR-TB is 24-30 months, with 6-12 months intensive phase (IP) and 18 months continuation phase (CP).
    - Change from IP to CP will be done only after achievement of culture conversion, i.e. two consecutive negative cultures taken at least 1 month apart. In case of delay in culture conversion, the IP can be extended from 6 months up to a maximum of 12 months.
    - Direct observation of treatment remains even more crucial, as this is the last chance at successful treatment that these patients will have.

7. Endometriosis in Urology

- Endometriosis is defined as the presence of functional endometrial tissue in an ectopic site. Endometriosis is usually confined to the ovaries, uterosacral ligaments, and cul-de-sac, but has been reported in almost every organ system.
- It may affect 10% to 20% of women of reproductive age, with a peak incidence in the mid-20s.
- Genitourinary endometriosis is rare, with involvement of the urinary tract in 1% to 5%. Endometriosis of urinary tract is predominantly involves the bladder (70% to 80%). Ureter is involved in 15% to 20% of cases of urinary tract endometriosis. Renal and urethral involvement is very rare.
- Ureteral involvement may be either intrinsic or extrinsic:
    - Intrinsic endometriosis is characterized by endometrial glands and stroma within the lamina propria, tunica muscularis, or ureteral lumen. Accounts for 20% of ureteral involvement.
    - Extrinsic endometriosis is localized within periureteral tissue. Eighty percent of ureteral involvement is extrinsic and mainly involves distal ureter.
    - Left side is more often affected, and bilateral disease occurs in up to 23%.
- Vesical endometriosis is usually solitary and typically involves the dome of the bladder.
- **Clinical features**
    - Up to one third of patients may be asymptomatic.
    - Classic symptoms and signs include cyclical flank pain, dysuria, urgency, UTI, and hematuria. Symptoms are commoner in intrinsic endometriosis.
    - Cyclical lower urinary tract symptoms, abdominal and pelvic pain are common with bladder involvement.
- **Evaluation**
    - **As 1/3rd** (25% to 43%) **of patients with ureteral endometriosis can have asymptomatic obstruction leading to** silent loss of renal function, **upper tract imaging is recommended in all patients with pelvic endometriosis.**
    - USG is readily available initial non-invasive imaging to look for HUN.
    - IVU is a better imaging test when the index of suspicion for ureteral involvement is high. Ureteral filling defects suggest intrinsic disease, while smooth strictured ureteral segments are seen with extrinsic disease.

  - RGP, CT urography, and MRI may help to ascertain the exact location and volume of the disease and provide valuable information for planning treatment. MRI is particularly useful for detection of ureteric and/or bladder deep pelvic endometriosis.
  - Cystoscopy and possible biopsy should be done in women with pelvic endometriosis, presenting with LUTS, and in those with hematuria. Ureteroscopy and possible biopsy should be performed when upper tract involvement is suspected.
- **Treatment**
  - **Goals**
    - i. Preservation of renal function
    - ii. Long-term relief of urinary obstruction
    - iii. Management of the ongoing disease process (Complete excision or ablation of endometriotic and reactive fibrotic tissue)
    - iv. Maintenance of fertility
    - v. Relief of symptoms with least invasive methods of treatment
    - vi. Individualized treatment according to age, reproductive desire, symptom severity, extent of lesion, and organ(s) involved
  - **Observation:** Patient can be observed only hormone therapy if renal function is normal and there is minimal to mild HDN with no functional obstruction (on renogram). GnRH agonists are used for ovarian hormonal ablation. Patients with intrinsic ureteral disease and extensive endometriosis are not good candidates for hormone only treatment.
  - **Surgical intervention:** is the treatment of choice for most patients with significant HUN and those with extrinsic disease.
    - i. If future pregnancy is not desired, treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO).
    - ii. If pregnancy is desired in future
      - Hormonal treatment combined with stenting is an option for ureteral involvement. Patient can be kept on stent changes until pregnancy is achieved, following which definitive treatment should be pursued. Some patient may not even need further surgical treatment with this approach.
      - Unilateral oophorectomy with or without ureterolysis
      - Ureterolysis alone especially for extrinsic disease. For laparoscopic ureterolysis transperitoneal approach is preferable as it allows better assessment of endometrial implants.
      - In small volume intraluminal/intrinsic endometriosis, ureteroscopic resection or ablation is an option. However, for extensive disease and for failed endoscopic resection distal ureterectomy with reimplantation is the performed procedure. This can be done by an open surgical, laparoscopic- or robotic-assisted approach, and has excellent long-term results with regard to renal preservation.
    - iii. **Surgical treatm**ent of vesical endometriosis depends on extent and depth of disease. Superficial involvement can be treated with TUR. Invasive/deep disease is best treated with open surgical, robotic, or laparoscopic partial cystectomy.

8. Bacterial resistance to antibiotics

- Definition: Antibiotic resistance is the ability of a microorganism to withstand or resist the effects of an antibiotic that was previously used to treat them. Today, almost all important bacterial infection in the India and throughout the world are becoming resistant to antibiotics.
- Bacterial infections which contribute most to human mortality and morbidity are also those in which emerging antimicrobial resistance is most obvious e.g. diarrhoeal diseases, respiratory infections, meningitis, STDs, and hospital-acquired infections.

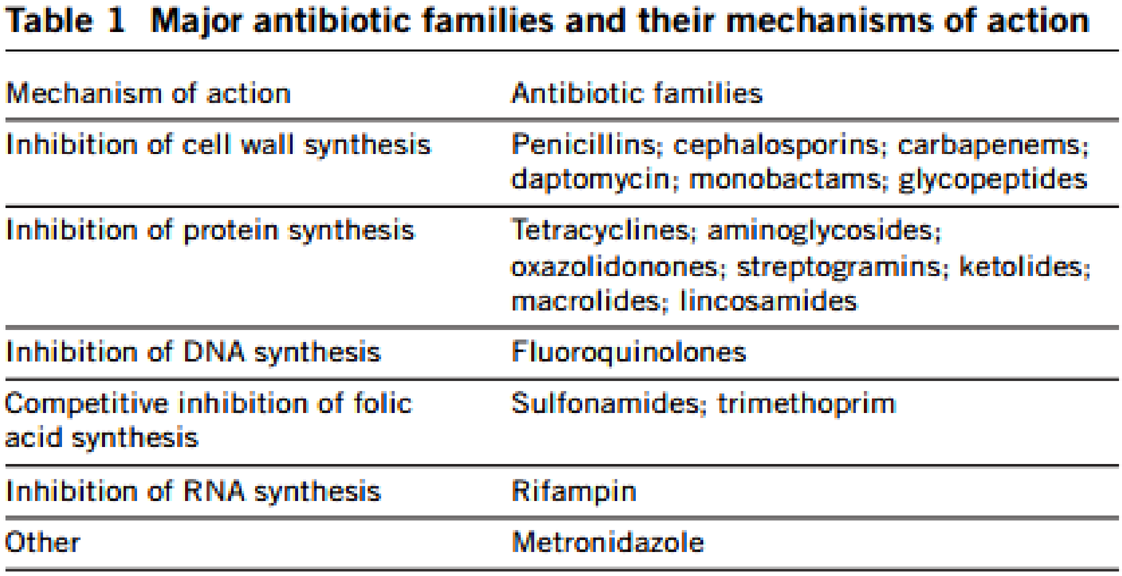
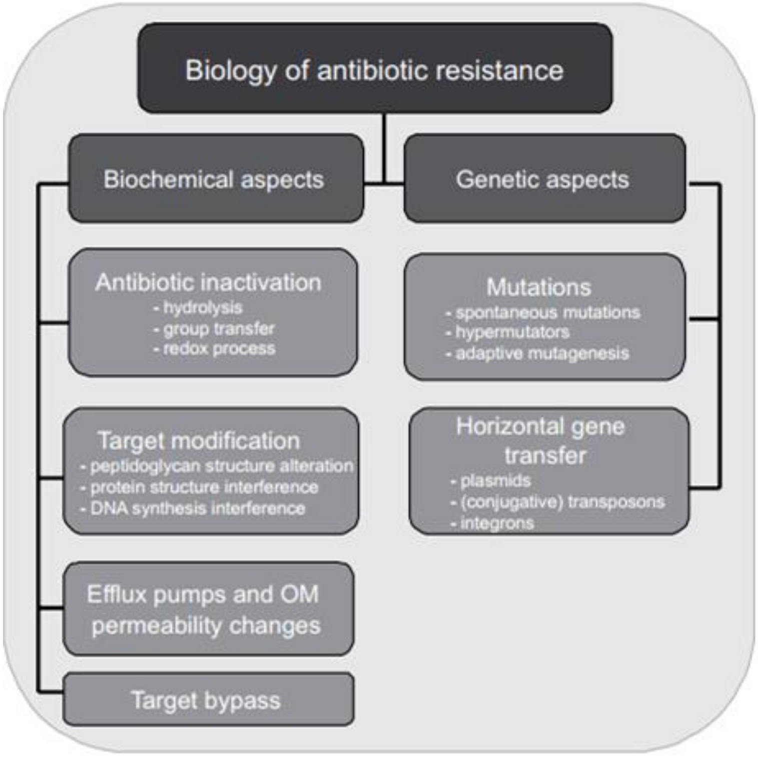


Table 1 Major antibiotic families and their mechanisms of action

Mechanism of action	Antibiotic families
Inhibition of cell wall synthesis	Penicillins; cephalosporins; carbapenems; daptomycin; monobactams; glycopeptides
Inhibition of protein synthesis	Tetracyclines; aminoglycosides; oxazolidonones; streptogramins; ketolides; macrolides; lincosamides
Inhibition of DNA synthesis	Fluoroquinolones
Competitive inhibition of folic acid synthesis	Sulfonamides; trimethoprim
Inhibition of RNA synthesis	Rifampin
Other	Metronidazole

- **Why does antimicrobial resistance develop?**
    1. Antibiotic treatment causes the micro-organisms to adapt or die. Incorrect use of antimicrobials increases the likelihood that bacteria and other microbes will adapt and replicate. This happens in various situations:
        - Pressure on the physicians to prescribe antimicrobials (even when they are not needed)
        - Incomplete treatment on the part of patient i.e. compliance issues
        - Indiscriminate use in hospitals
        - Over-the-counter access to antibiotics in many countries
- **Mechanisms of AMA resistance**
    1. Antibiotic inactivation
        - This includes direct inactivation of the active antibiotic molecule.
        - Occurs by production of enzymes that degrade or modify the drug itself.
        - Cephalosporine and penicillin resistance by beta-lactamases and ESBLs
    2. Target modification
        - Involves alteration of the sensitivity to AMA by modification of the antibiotic target site so that AMA is unable to bind properly.
        - Example: Acquisition of penicillin-binding protein-2 (PBP-2) by Staphylococcus aureus results in resistance to methicillin (MRSA).
        - Mutations in different subunits of RNA results in resistance to AMA that act by inhibition of protein synthesis at different levels e.g. aminoglycosides, tetracyclines, macrolides, chloramphenicol, and oxazolidinones (Linezolid, cycloserine)
    3. Efflux pumps and changes in the permeability of cell wall
        - Efflux pumps are the membrane proteins that export AMA out of the cell and keep its intracellular concentrations at low levels.
        - Reduced cell wall permeability results in reduced antibiotic uptake.
        - This results in overall low concentration of drug inside the bacteria.
        - This mechanism may affect all classes of antibiotics, especially macrolides, tetracyclines, beta lactams, and fluoroquinolones.



        4. Target bypass
            - Some bacteria become refractory to specific antibiotics by bypassing the inactivation of a given enzyme. This mode of resistance is observed in many trimethoprim- and sulfonamide-resistant bacteria.
        5. Mutation
            - Specific spontaneous or acquired mutation at different levels followed by natural selection is another mechanism
            - Reported in E.coli, MTB, P. aeruginosa
        6. Horizontal gene transfer
            - Involves acquisition of resistance genes from other microorganisms conjugation, transformation, or transduction
            - Resistance gene can confer resistance by various means described above
            - Classical example is that of E. coli

- **AMA resistance of urological significance**
    1. **MRSA**
        - MRSA is resistant to penicillin-like beta-lactam antibiotics.
        - Drugs that are still active against MRSA: Glycopeptides (vancomycin and teicoplanin), linezolid, tigecycline, and daptomycin
    2. **VRE (Vancomycin-Resistant Enterococci)**
        - VRE cause UTI and sepsis and UTIs mostly among patients in hospitals
        - VRE remains a major threat, because only a few antimicrobial options are available to treat VRE including linezolid and quinupristin/dalfopristin
    3. **DR-TB, MDR-TB and XDR-TB**
        - Refer to previous questions on GUTB and XDR-TB
    4. **CRO (Carbapenem-Resistant Organisms)**
        - CROs have become resistant to “all or nearly all” available antibiotics, including carbapenems, which are typically reserved as the “treatment of last resort”
        - An enzyme called New Delhi metallo-beta-lactamase-1 (NDM-1) is present in some gram-negative Enterobacteriaceae and confer this type of resistance
        - Two most common types of CROs are carbapenem-resistant *Klebsiella* species and carbapenem-resistant *E. coli.*
    5. **ESBL-Producing Enterobacteriaceae**
        - ESBL-producing Enterobacteriaceae carry a broad-spectrum beta-lactamase enzyme that enables them to become resistant to a wide variety of penicillin and cephalosporin antibiotics.
        - Some ESBL-producing Enterobacteriaceae are resistant to nearly all antibiotics of penicillin and cephalosporin classes. In such cases, the remaining treatment option is a carbapenem (meropenem, ertapenem). However, these drugs should be used with caution, since use contributes to resistance.
    6. **Others**
        - Drug resistant *N. gonorrhoea and P. aeruginosa* are also important cause in urology
- **Consequences of AMA resistance**
    - Prolonged illness and longer periods of infectivity
    - Increased cost of further treatment: related to prolonged treatment duration, use of next level of costlier drugs, use of multiple drugs to treat resistant bacteria, and cost of management of complications. Major example of this is the treatment of MDR-TB which is more than 100 times than the standard treatment of TB.
    - Increased burden to healthcare facilities
    - Compromises the success of treatments e.g. organ transplantation, cancer chemotherapy and major surgeries.
- **Prevention**
    - Avoid overuse and misuse of antibiotics by guideline based use of AMA
    - Ensure complete and adequate treatment at the level of the patient (e.g. DOTS for TB)
    - Prevent infections to reduce the overall use of antibiotics
    - Education of patients and health care professional bout AMA resistance
    - Improve surveillance of antibiotic-resistant infections by timely audits
    - Report antibiotic-resistant infections to surveillance teams.

9. Nosocomial UTI (NUTI)

- **Definition**
    - A UTI is said ‘nosocomial’ or ‘nosocomially acquired’ (NUTI or NAUTI) when it is acquired in any healthcare institution or, more generally, when it is related to patient management. Virtually, all healthcare-associated UTIs are caused by instrumentation of the urinary tract. Catheter-associated UTIs are commonly called CAUTI.

- **Epidemiology**
    - NUTI is one of the most frequent infections and it is responsible for more than 40% of all nosocomial or healthcare-associated infections (HAIs).
    - Most common causes of NUTI are indwelling urethral catheterization (80%) or genitourinary / urological manipulation (10-20%).
    - Rate of CAUTI with catheterization
        - One-time catheterization: 1-5%
        - Indwelling catheter with closed drainage: 20%
        - Indwelling catheter with open drainage: 100%
    - Rate of CAUTI also depends on duration of catheterization as there is 3% increase in risk per day of catheterization, which reaches to 100% at one month.
    - Morbidity and mortality from CAUTI are considered to be relatively low compared to other HAIs.
- **Pathogenetic mechanisms**
    - Urethral catheters
        - Bacteria can enter the urinary tract at the time of catheter insertion especially if patient has inadequate cleansing of the perineum and meatus.
        - Microorganisms can ascend from perineum to urethra and to catheter's outer surface. Indwelling urethral catheter allows continuous access of organisms into the urinary tract by increasing urethral colonization by uropathogens, especially in women.
        - Urethral catheter can inhibit or bypass normal defence mechanisms that would normally prevent or minimize bacteria-epithelial cell interactions e.g. glycosaminoglycan (GAG) layer and biofilm formation, thus protecting the bacteria.
        - Failure in the draining system→ open/closed
    - Hematogenous or lymphatic dissemination
        - Most common microorganisms in this particular scenario are: S. aureus, Candida, Salmonella and some species of Pseudomonas.
        - Hematogenous dissemination usually occurs as a consequence of a systemic disease with kidney as target organ.
- **Risk factors for CAUTI**
    - Prolonged duration of catheterization
    - Lack of urinometer usage
    - Collector bag colonized by microorganisms
    - Advanced age
    - Diabetes mellitus
    - Renal failure
    - Female gender
    - Incorrect catheter care
    - Debilitating disease
    - Immunocompromised status
- **Causative organisms**
    - Majority of nosocomial CAUTIs are produced by bacteria which come from patient's own colon, and perineum which is known as endemic infection. Most common organism is E. coli. Other common organisms include Klebsiella, Pseudomonas and Candida species.
    - Epidemic or secondary infection occurs from contaminated equipment such as cystoscopes, irrigation solutions or disinfectants used for cleaning before catheter insertion, and cross-transmission through hospital personnel's hands.
- **Prevention of NUTI**
    - Correct insertion techniques and catheter care measures
    - Urinary catheters should be used only when necessary and left in place only for as long as necessary
    - Hand washing and disinfection
    - Using sterile equipments for urologic instrumentation
    - Catheters should be appropriately fixed to avoid urethral traction
    - Use of closed drainage system
    - Avoid break in closed drainage system
    - Avoid blocking of catheter
    - Avoid irrigation unless needed

  - Meatal care with povidone-iodine should be **avoided**
  - Catheters should **not** be changed at fixed intervals
  - Separate infected and uninfected patients

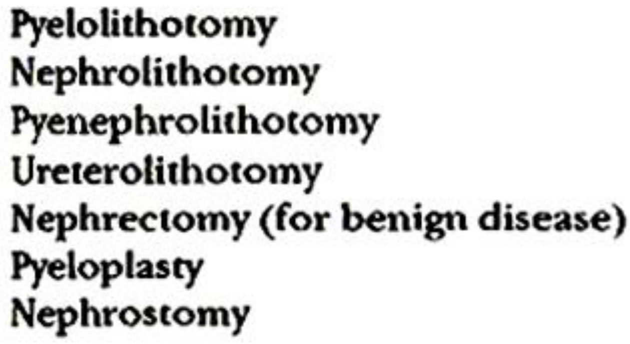
10. **Urological manifestations of sarcoidosis (Use hyperlinks please)**
    - **Indian J Urol- 2017**
    - **J Urol- 2012**

11. **Urological manifestations of HIV**
    - **UCNA- 2008 :** HIV-AIDS – Urologic Considerations. Urol Clin N Am 35 (2008) 59–68.

2. Dorsal lumbotomy indications and approach

Indications-

- pediatric patients
- thin adults requiring bilateral nephrectomy.
- These surgeries can be done



Pyelolithotomy
Nephrolithotomy
Pyenephrolithotomy
Ureterolithotomy
Nephrectomy (for benign disease)
Pyeloplasty
Nephrostomy

Steps-

- Anesthetized and intubated in the supine position.
- Shifted to prone position (ventral decubitus/ventral recumbent position).
- To avoid axillary plexus injury, the humerus should not be forced into the axilla.
- The elbow should be flexed 90 degrees and padded to prevent ulnar nerve injury.
- A vertical skin incision is made from the inferior border of the 12th rib to the iliac crest, in line with the lateral border of the sacrospinalis muscle.
- The subcutaneous tissues are divided, exposing the latissimus dorsi muscle.
- The aponeurosis of the latissimus dorsi is separated from the posterior layer of the lumbodorsal fascia where it overlies the sacrospinalis muscle.
- The posterior layer of the lumbodorsal fascia, is incised and sacrospinalis muscle to be retracted medially. The costovertebral ligament is divided for retraction of the 12th rib,
- The fused middle and anterior layers of the lumbodorsal fascia are divided for the quadratus lumborum muscle to be retracted medially. The ilioinguinal nerve should be identified and spared.
- Entry into the paranephric space is achieved by incising the transversalis fascia.
- Division of the perinephric fascia reveals the kidney.

*3. Benchekroun procedure

Hydraulic valve– Benchekroun nipple is a type of Continent urinary diversion.

- In this procedure a small bowel segment is isolated, with subsequent reversed intussusception that effectively apposes the mucosal surfaces of the segment.
- Tacking sutures are placed on a portion of the circumference of the intussuscepted
- segment to stabilize the nipple valve while allowing urine to flow freely between the leaves of apposed ileal mucosa. As the pouch fills, hydraulic pressure closes the leaves, thereby ensuringcontinence.
- The premise of this technique is that as the reservoir fills, the pressure within the valve would also increase, resulting in continence.
- Concerns regarding stomal stenosis, especially in children, and nipple destabilization have resulted in this procedure being largely abandoned.

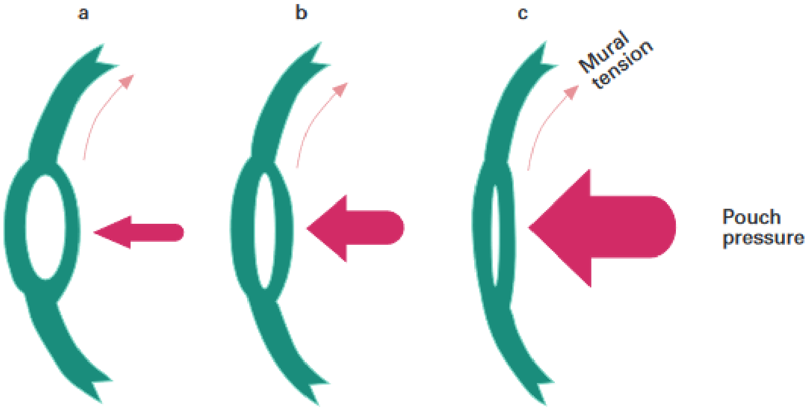


Fig. 6. The mechanisms of continence. The mural tension and intra-pouch pressure increase with pouch filling, thus closing the valve (arrows).

4. Mainz II pouch

A variation of ureterosigmoidostomy, the sigma-rectum or the Mainz II pouch, creates a low-pressure rectosigmoid reservoir of increased capacity.

INDICATIONS FOR SURGERY:

- Primary urinary diversion,
- Revision of ureterosigmoidostomy,
- Conversion of incontinent diversion.
- Patients with bladder exstrophy or after radical cystectomy for bladder cancer.

CRITERIA : A competent anal sphincter and no renal insufficiency (creatinine maximum 1.5 mg per dL).

CONTRAINDICATIONS: Incompetent anal sphincter, irradiation of the pelvis, diverticulosis of the sigmoid colon, polyposis, and a serum creatinine greater than 1.5 mg%.

TECHNIQUE:

- Access is gained by a median laparotomy as for ureterosigmoidostomy.
- For creation of the pouch, the intestine is opened at the anterior taenia starting from the rectosigmoid junction over a total length of 20 to 24 cm distal and proximal of this point
- The intestine is positioned in a shape of an inverted U. The posterior wall of the pouch is closed by side-to-side anastomosis of the medial margins of the U using two-layer running sutures of 4-0 polygalactin for the seromuscular layer and 5-0 polygalactin for the mucosa
- The left ureter is pulled through retromesenterically to the right side
- For ureteral implantation the mucosa is incised and the seromuscular layer is excised between the two cranial stay sutures to create a wide button hole type of opening as an entrance of the ureter into the pouch.
- 6 Fr ureteral stents are inserted into the ureters and are pulled out through the anus with the rectal tube, which is afterward reinserted.
- Closure of the anterior pouch wall is performed in two layer sutures (5-0 polygalactin for the seromuscular and 4-0 polygalactin for the mucosal layer)

Complications :

- Early: Dislodged ureteral stent, pneumonia, pulmonary embolism, wound dehiscence, and ileus necessitating surgical intervention.
- Late complications: Ureteral stenosis , Nephrolithiasis ,Rupture of the anterior suture line required temporary colostomy, Perianal bleeding, Pyelonephritis, metabolic acidosis

5. Uretero-colonic anastomosis techniques-

Nonrefluxing & Tunneled-

- Leadbetter and Clarke
- Transcolonic Technique of Goodwin
- Strickler
- Pagano

Refluxing & Non-tunneled-

- Cordonnier
- Nesbit

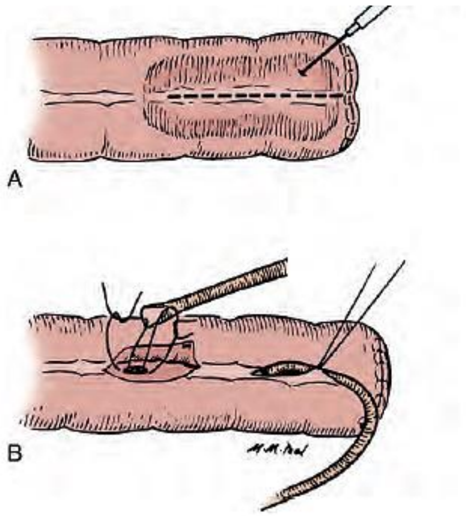


Figure 97-21. Leadbetter-Clarke ureterointestinal anastomosis. A, Injection of the submucosal tissues with saline facilitates the dissection. B, A linear incision is made in the taenia, the taenia is raised, and the mucosa is identified. A small button of mucosa is removed, and the ureter is spatulated and then sutured to the mucosa with 5-0 polydioxanone sutures. The seromuscular layer is sutured over the ureter, with care taken not to compromise or occlude the ureter.

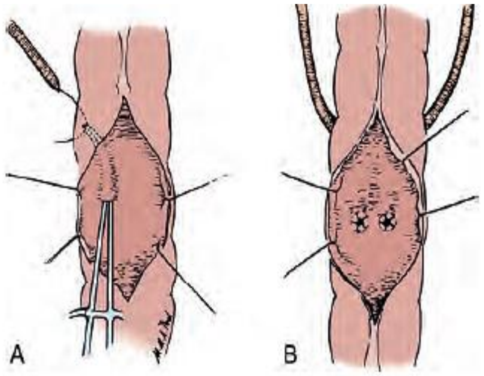


Figure 97-22. Transcolonic technique of Goodwin. A, The bowel is opened on its anterior surface; a small rent in the mucosa is made; and with a mosquito hemostat, the mucosa is raised from the submucosa extending laterally. A 3- to 4-cm tunnel is made before the clamp exits the serosal wall. The ureter is grasped and pulled into the submucosal tunnel. B, Both ureters have been drawn into the bowel through their submucosal tunnels before each is spatulated and circumferentially sutured to the mucosa. These sutures should also incorporate a portion of the muscularis for security. Where the ureter enters the colonic sidewall adjacent to the mesentery, the adventitia of the ureter is secured to the colonic serosa with interrupted 5-0 polydioxanone sutures.

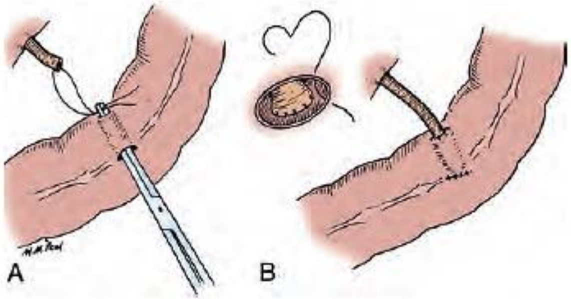


Figure 97-23. Strickler ureterointestinal anastomosis. A, A small linear incision is made in the taenia, and the submucosa is dissected from the mucosa laterally. After a distance of 3 to 4 cm has been achieved, a small hole is made in the serosa and the ureter is drawn through. B, A button of mucosa is excised, and the ureter is spatulated and sutured to the mucosa with 5-0 polydioxanone sutures. The rent in the taenia is closed with interrupted sutures, and an adventitial suture at the ureter's entrance point into the colon secures it to the serosa of the colon.

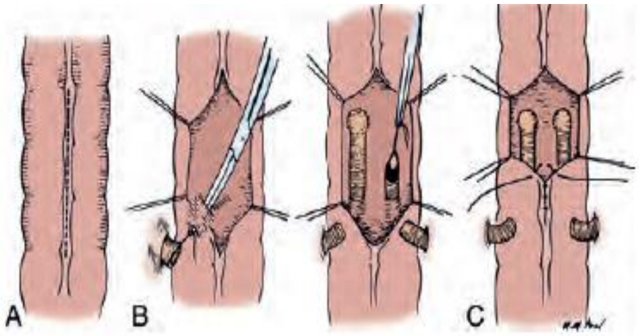


Figure 97-24. Pagano ureterointestinal anastomosis. A, A linear incision is made in the taenia between 4 and 5 cm in length. B, The submucosa is dissected from the mucosa laterally on both sides to the level of the mesentery. The ureters are drawn into the submucosal tunnel distally and sutured to the mucosa with 5-0 polydioxanone sutures proximally. C, The serosa is reapproximated, with incorporation of the mucosa in the midline.

6. Gastrocystoplasty

- The use of stomach in the bladder facilitates net excretion of chloride ions, which in turn supports a main buffer system of the urine (ammonium chloride).
- This permits secretion of acid without the use of titratable acids that potentially leads to the depletion of the buffer systems.
- Ammonia resorption does not occur either, as has been observed when large and small bowel are used in the urinary tract.

Indications-

- no other type of bowel was available for urinary reconstruction - those with previous radiation and those with absence of large bowel or reduced small bowel (the cloacal exstrophy group).
- Patientswith metabolic acidosis, as this condition would be exacerbated by the addition of large or small bowel because of chloride or ammonia resorption.

Steps-

- The bladder is filled to a pressure of approximately 20cm of water and the detrusor incised in the midline sagittal plane. Great care is taken to preserve the transitional epithelium in finding the plane between the transitional epithelium and muscularis
- Usually remove muscularis from twothirds to three-quarters of the anterior and lateral wall of the bladder. The bladder is emptied by lowering the reservoir, followed by gentle packing with moist sponges. An alternative technique is to use a large balloon catheter (Helmstein balloon) to facilitate this dissection. This can be left in place following the surgery to promote healing of the epithelium to the seromuscular flap.
- A gastric flap is obtained. Before it is brought into the pelvis, however, the mucosa is removed. This is done very easily by removing the staples and placing four quadrant sutures for traction so the flap is opened as a parallelogram.
- A vascular loop is gently placed around the pedicle with enough traction so that the blood supply to the pedicle is temporarily interrupted.
- sharply dissect the mucosa from the muscularis-Potts tenotomy scissors are used for this purpose. The proper plane, which is easily found, tends to have a somewhat foamy appearance
- Once the mucosa is removed the pedicle vascular loop is loosened and bleeders are electrocauterized using the bipolar cautery. Most of the bleeding will be in the midline where the perforators follow the gastroepiploic pedicle.
- The demucosalized flap is brought into the pelvis as with any augmentation. The demucosalized flap is then laid directly on top of the outside of the bladder epithelium raw surface to raw surface.
- Either a Penrose drain or a suction drain is then placed between the transitional epithelium and flap and brought out through the abdominal wall. This will be removed in approximately 48 hours.
- The demucosalized gastric flap is sutured in place using a running, locking 3-0 Vicryl suture as a single layer closure.
- In an effort to keep the contact between the transitional epithelium and the demucosalized gastric flap the bladder is kept partially filled at approximately 20cm water pressure using a vented drainage system. This system is maintained for approximately five to seven days.
- Subsequently, the patient is placed on either intermittent catheterization or intermittent clamping of a suprapubic tube

7. Techniques of percutaneous access in PCNL

Percutaneous approach to the kidney was first used by Goodwin and colleagues in 1955 for the drainage of obstructed kidney and Fernstrom and Johansson in 1976 reported first percutaneous removal of renal stone.

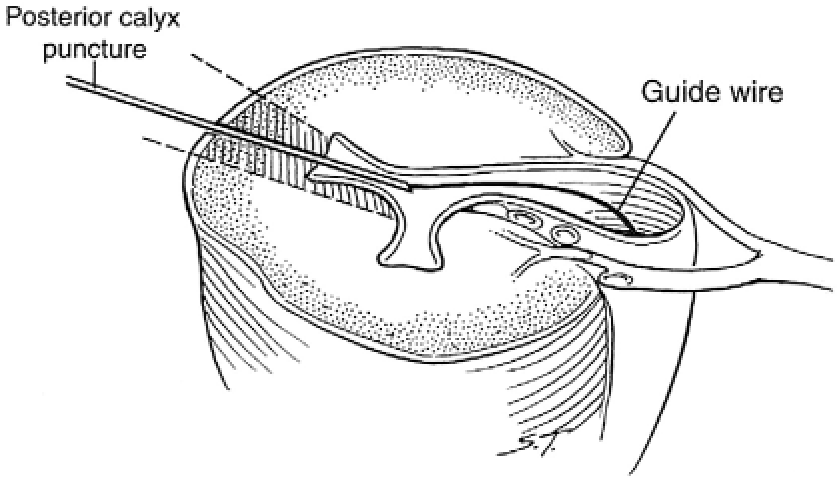


FIG. 1. Preferred site for percutaneous access is through posterior calix. This approach facilitates negotiation of wire out of calix and into ureter, and may decrease risk of vascular injury since access tract is created along avascular field between anterior and posterior divisions of renal vasculature, known as Brödel's bloodless line.

Remember…

Lingeman's Law for Management of Nephrolithiasis

If the stone problem is simple, any intervention will be successful.
If the stone problem is complex, perform percutaneous nephrolithotomy.

---

1. **Blind access** for drainage of the obstructed kidneys in emergency cases or when catheter placement for retrograde injection of a contrast medium for PCNL is not possible. Blind approach first reported for access to the system in PCNL, especially in severely hydronephrotic kidneys, is a potential alternative for experienced surgeons for reducing radiation exposure.
2. **Flouroscopy guided puncture** for renal access should be medial to the posterior axillary line to avoid injury to the colon because the position of the colon is usually anterior or anterolateral to the most lateral part of the kidney.
   The two techniques of fluoroscopic puncture best described are "eye of the needle" (Bullseye) and "triangulation". Both consist of several steps where C-arm fluoroscopy is rotated into different positions relative to the needle and the target (contrast-filled).
3. **Ultrasonography-guided access**, location of the target calyx is identified in the transverse and sagittal planes by real-time ultrasonography. Ultrasonography is particularly useful in ectopic , malrotated kidneys and in children.
4. **CT guided percutaneous access** has been reported to be feasible alone or with fluoroscopy. used in cases with an unfavorable body habitus or known retrorenal posterior organs, it requires a suitable setup in the radiology suite and/or specialized equipment, and access is performed with the patient awake and as a procedure separate from actual percutaneous nephrolithotomy .

5. **Ureteroscopic-guided percutaneous renal access.**
    - Consists in gaining access under ureteroscopic vision with the use of the flexible ureteroscope.
    - The patient is in the prone position and the desired calyx is chosen under ureteroscopic vision.
    - Puncture to the calyx is done under fluoroscopic guidance until the tip of the needle is seen by the ureteroscope
    - It may be advantageous for nondilated caliceal systems, complex stone burdens, ectopic or malrotated kidneys, and for morbidly obese patients, where the traditional puncture is almost always difficult.

6. **Robotic system to access the renal collecting system** for PCNL consisted of a manually positioned robotic arm mounted on the operating table, guided by C-arm fluoroscopy eg., PAKY (percutaneous access to the kidney) and PAKY-RCM (remote center of motion) system.

8. Saline TURP

Saline can be used in bipolar systems, such as the Gyrus ACMI (Maplegrove, Minnesota), Olympus® andStorz™ systems.

The **TURis bipolar resection system** differs from monopolar resection in that the tissue effect takes place between two electrodes that are part of the same device. The active and return electrode are within the resectoscope, forming a bipolar electrosurgical system. Due to the conductive saline, only a very small fraction of the current passes through the tissue, and no neutral electrode is required.

Another form of bipolar technology is the **Gyrus PlasmaKinetic** (PK) Tissue Management System (Olympus Surgical Technologies America, Maple Grove, MN), wherein energy is initially transmitted from the loop into the surrounding saline. The saline is vaporized into gas around the loop, with additional energy from the loop then converting the gas to plasma. The excited sodium ions of the plasma give this technology the characteristic orange glow. Once created, the plasma molecules are able to be excited for use in resection. This seems like a dynamic and explosive process, but it actually allows tissue resection at lower temperatures with a lower voltage.

Some Points:

Saline is chosen because Low resistant electrolyte medium

Saline - 40 ohms -→ Lowest
Glycine - 800 ohms
Water - 1600 ohms
Tissue - 500 ohms
Blood vessel - 125 ohms

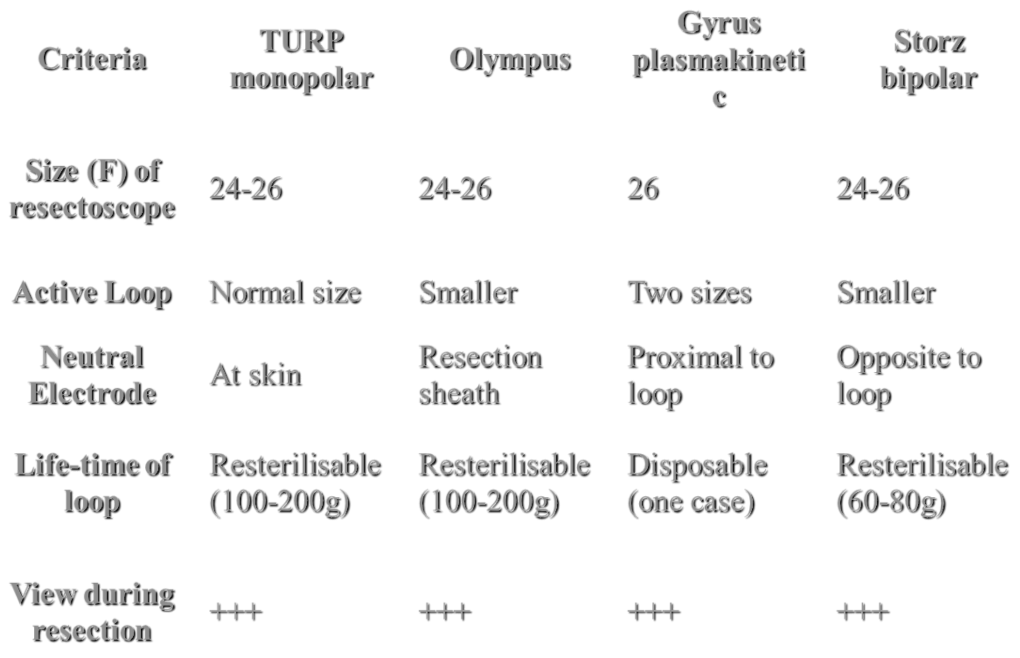
Once discharge started that can be maintained till output <100 W

Low risk of depth penetration

- Heated sheath injury low.
- Tissue (protein) cut by >215*c
- carbonization >420*c
- TURis - 300-400*c

Advantages-

- Collateral and penetrative tissue damage is reduced compared to standard monopolar TURP surgery & less granulation tissue is formed
- Less tissue charring occurs, which helps in identifying the surgical capsule and other landmarks.
- Negates the need for diathermy pad
- Unwanted stimulation of the obturator nerves and cardiac devices avoided
- Performing TURP with saline eliminates the possibility of TUR syndrome, so limitations in gland size and procedure time also are eliminated
- The resected prostate chips are cleaner and have less coagulation or desiccation defects, which simplifies pathological examination.



Criteria	TURP monopolar	Olympus	Gyrus plasmakinetic	Storz bipolar
Size (F) of resectoscope	24-26	24-26	26	24-26
Active Loop	Normal size	Smaller	Two sizes	Smaller
Neutral Electrode	At skin	Resection sheath	Proximal to loop	Opposite to loop
Life-time of loop	Resterilisable (100-200g)	Resterilisable (100-200g)	Disposable (one case)	Resterilisable (60-80g)
View during resection	+++	+++	+++	+++

10. Buccal mucosal graft

The use of buccal mucosa in urethroplasty in adults was first reported by El-Kasaby et al

GRAFT BIOLOGY

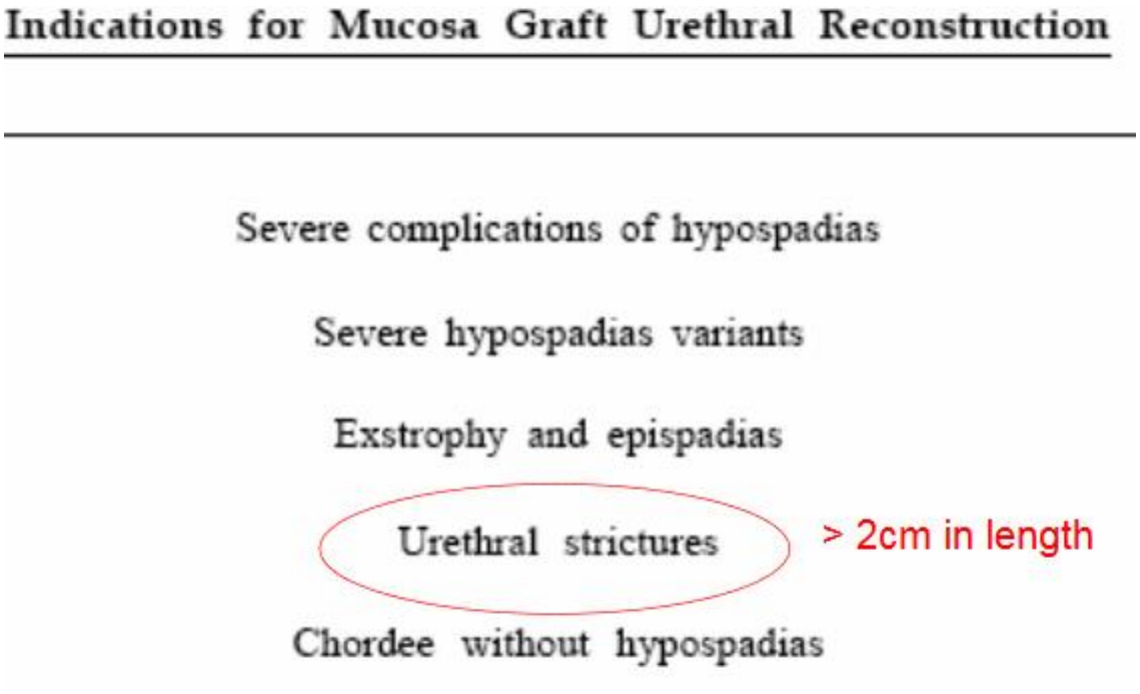
- IMBIBITION: diffusion of nutrients between donor and recipient site 1st 48hrs
- INOSCULATION: new blood vessel growth between recipient and donor graft 2-4 days

COMPLICATIONS WITH SKIN AND BLADDER GRAFTS

- Shrinkage
- Recurrent strictures
- Diverticuli (urine dribbling)
- Trapped urine
- Ejaculatory dysfunction
- Graft necrosis
- Fistulas

PRINCIPLES OF IDEAL MUCOSAL GRAFT -

1) well vascularized recipient site
2) rapid and efficient IMBIBITION
3) rapid and efficient INOSCULATION
4) immobilization of graft and recipient site as neovascularization and healing take place



Indications for Mucosa Graft Urethral Reconstruction

Severe complications of hypospadias

Severe hypospadias variants

Exstrophy and epispadias

Urethral strictures > 2cm in length

Chordee without hypospadias

ADVANTAGES OF BUCCAL MUCOSA GRAFTS

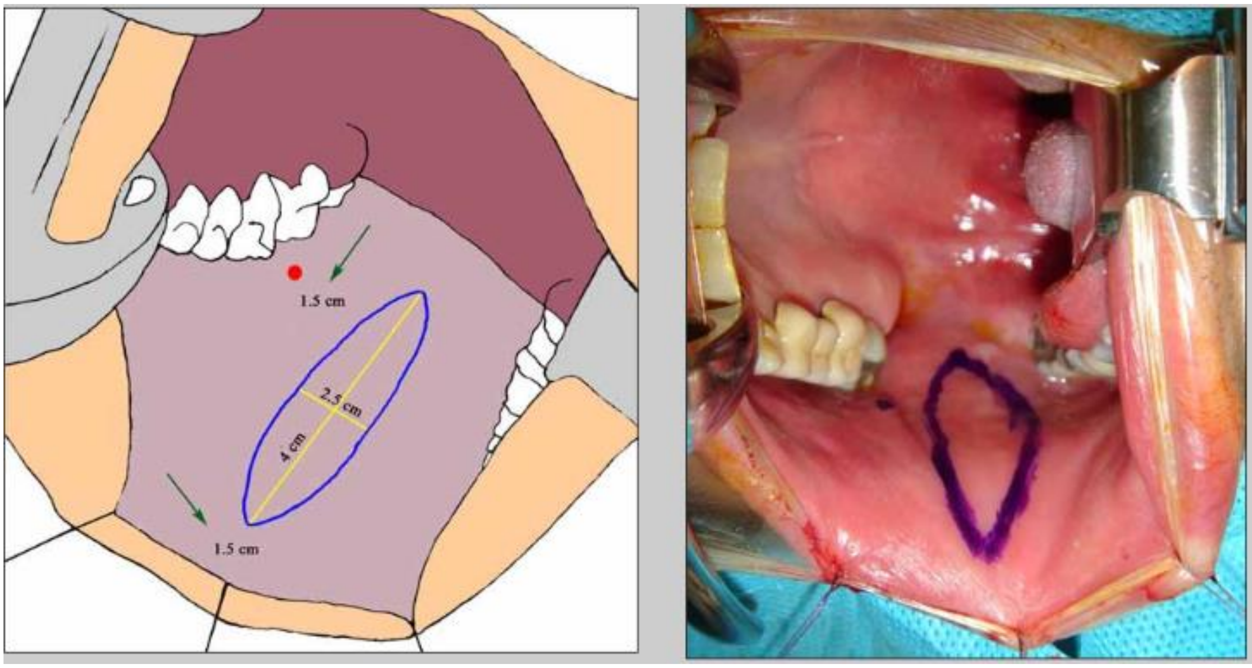
1) ease of application/harvest
2) hairless
3) multiple hairless donor source
4) wide versatiliy
5) rare sacculation
6) normal appearing conduit that closely resembles urethra
7) thick mucosa with thin lamina propria - good inosculation
8) Resistant to infection
9) Compatibility with wet environment

HISTOLOGY of BUCCAL MUCOSA

- Heavy infiltration of elastin - resilient and less likely to form diveriticuli
- Less shrinkage than bladder mucosa - can be used in 1:1 fashion
- Lamina propria has richer vascular network than skin or bladder mucosa - better insoculation

Harvesting oral mucosa from the mouth-

- Oral mucosal graft from the cheek-graft is harvested from the internal surface of the cheek
- Oral mucosal graft from the tongue-graft is harvested from the ventral surface of the tongue. Done when the harvesting from the cheek is not possible.



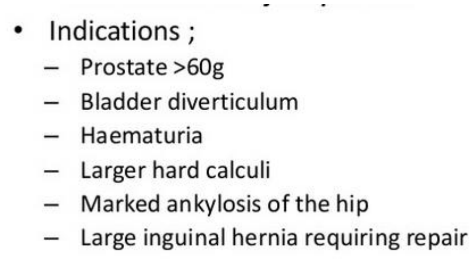
- Nasal intubation
- Extend neck
- Identify Stensen's duct -opposite 3rd molar
- 2 x 6-9 cm strip with indigo carmine
- 2 L retractors - sponge in mouth or 2 suture retractors, Dingman retractor.

- Infiltrate with 1% lido or 0.25% marcaine with epi
- Incise boundaries with 15 blade
- Elevate mucosa using plastics sharps
- Transect at anterior tonsillarpillar
- Soak in saline
- Leave donor site open or close with vicryl rapide.

COMPLICATIONS OF HARVEST

- Hemorrhage
- Infection
- Pain
- Swelling
- Damage to Stenson’s duct (Parotid)
- Perioral or cheek numbness

11. Millin's prostatectomy-



- Indications ;
  - Prostate >60g
  - Bladder diverticulum
  - Haematuria
  - Larger hard calculi
  - Marked ankylosis of the hip
  - Large inguinal hernia requiring repair

Steps – please read attached BJUI article

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Surgery Illustrated – Surgical Atlas
Millin Retropubic Prostatectomy

John M. Fitzpatrick
Mater Misericordiae University Hospital Dublin & University College Dublin, Ireland

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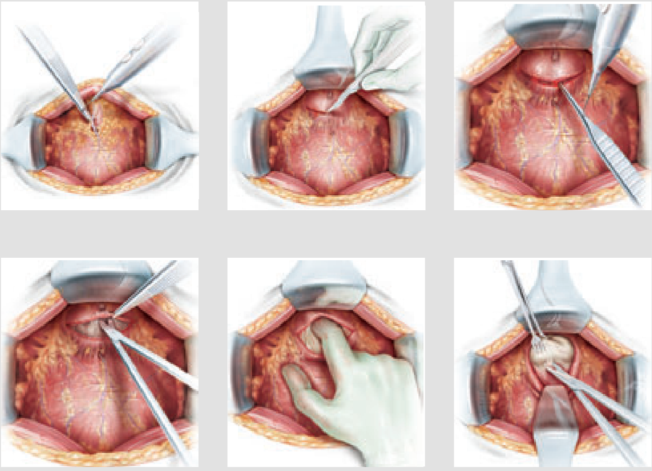

MILLIN RETROPUBIC PROSTATECTOMY

The operation which Terence Millin described in 1945, retropubic prostatectomy is a very enjoyable operation to perform, particularly because it uses established anatomical principles as the basis for the procedure. In fact, it is well worth reading his original description in the Lancet in 1945, because most of what he says there is still relevant today and is a clear and well-written exposition of the surgical technique. It is an easily performed procedure, which was revolutionary at the time of its introduction because instead of a transvesical approach, it involved a transcapsular dissection of the prostatic adenoma.

INDICATIONS AND PATIENT SELECTION

The usual indication given for performing a Millin's Prostatectomy is for patients with prostates which weigh more than 80 gms. The weight should be assessed by a combination of clinical examination and transrectal ultrasound. It might be felt by some that this is a rather low prostatic weight at which to abandon TURP, but in that case the indication would be a size greater than that which the urologist feels that a TURP would be accompanied in 60 minutes. In the present day, laser technology has allowed large prostates to be removed by methods other than TURP and some have even said that the era of the Millin Prostatectomy is therefore over. I very much disagree with this and would not like to see the demise of such a satisfying surgical procedure, with excellent outcomes for the patient.

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SURGICAL PROCEDURE

The patient is placed supine on the operating table, and a moderate amount of breaking of the table may be helpful in affording greater exposure in the pelvis. No special instruments are required, although Millin did advocate the use of a bladder-neck spreader (which was very uncomfortable for the assistant to use) and an instrument which was a modification of a vulsellum forceps which looked like an angulated Alis clamp.

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Figure 1

A Pfannenstiel incision is the standard approach, but some prefer a lower midline incision extending from umbilicus to pubic bone. A self-retaining retractor of the Forder or Finochietto variety is then inserted. There is usually fat lying on the prostate, and this can be removed by sweeping it away with a tissue forceps in an up and down direction. This prevents tearing of the veins, which would occur if the fat were removed side to side. The superficial dorsal vein is then exposed, and then diathermised or clipped and cut.

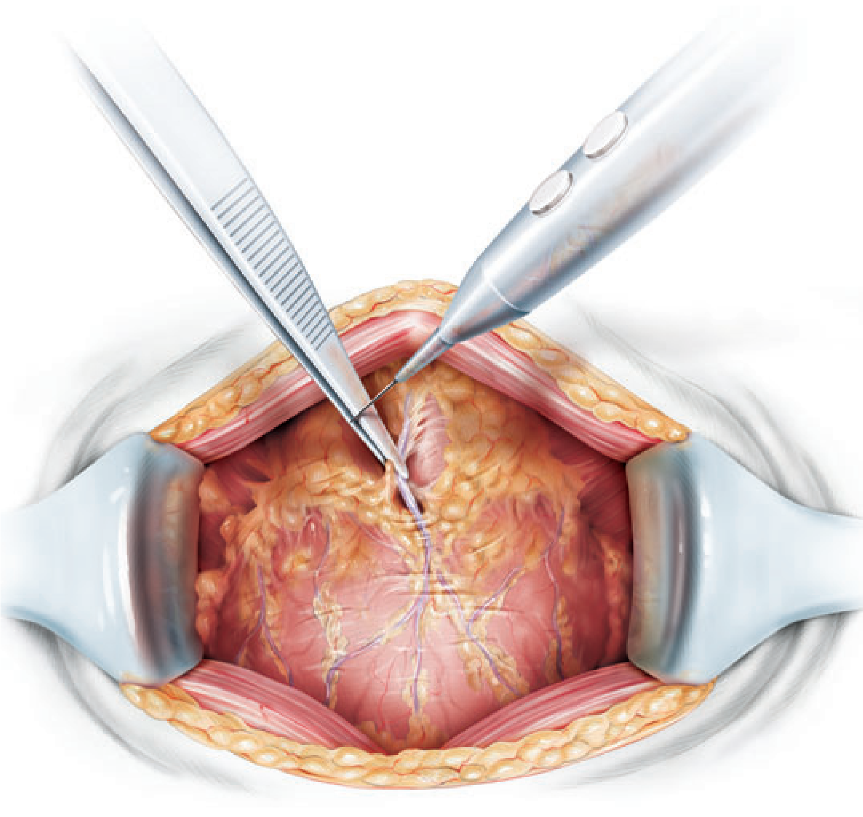

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Figure 2

The prostate can then be clearly seen. There is no need to put swabs on either side of the prostate, or to insert sutures into the lateral limits of the capsular incision. A transverse incision is made in the prostatic capsule 1cm distal to the bladder neck. This can be performed with a size 11 or 15 blade, or with the diathermy.

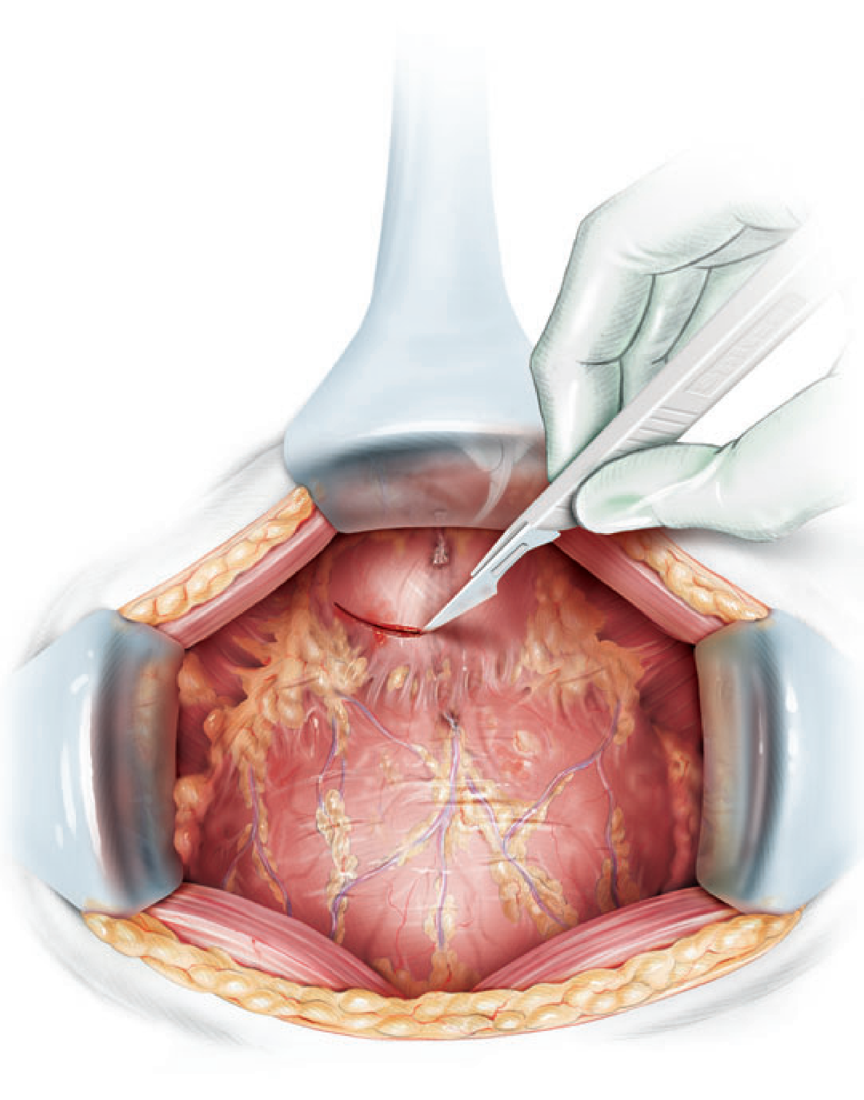

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Figure 3

There may be brisk bleeding from some sizeable capsular veins so great care should be taken to stop this bleeding with pinpoint accuracy with the diathermy.

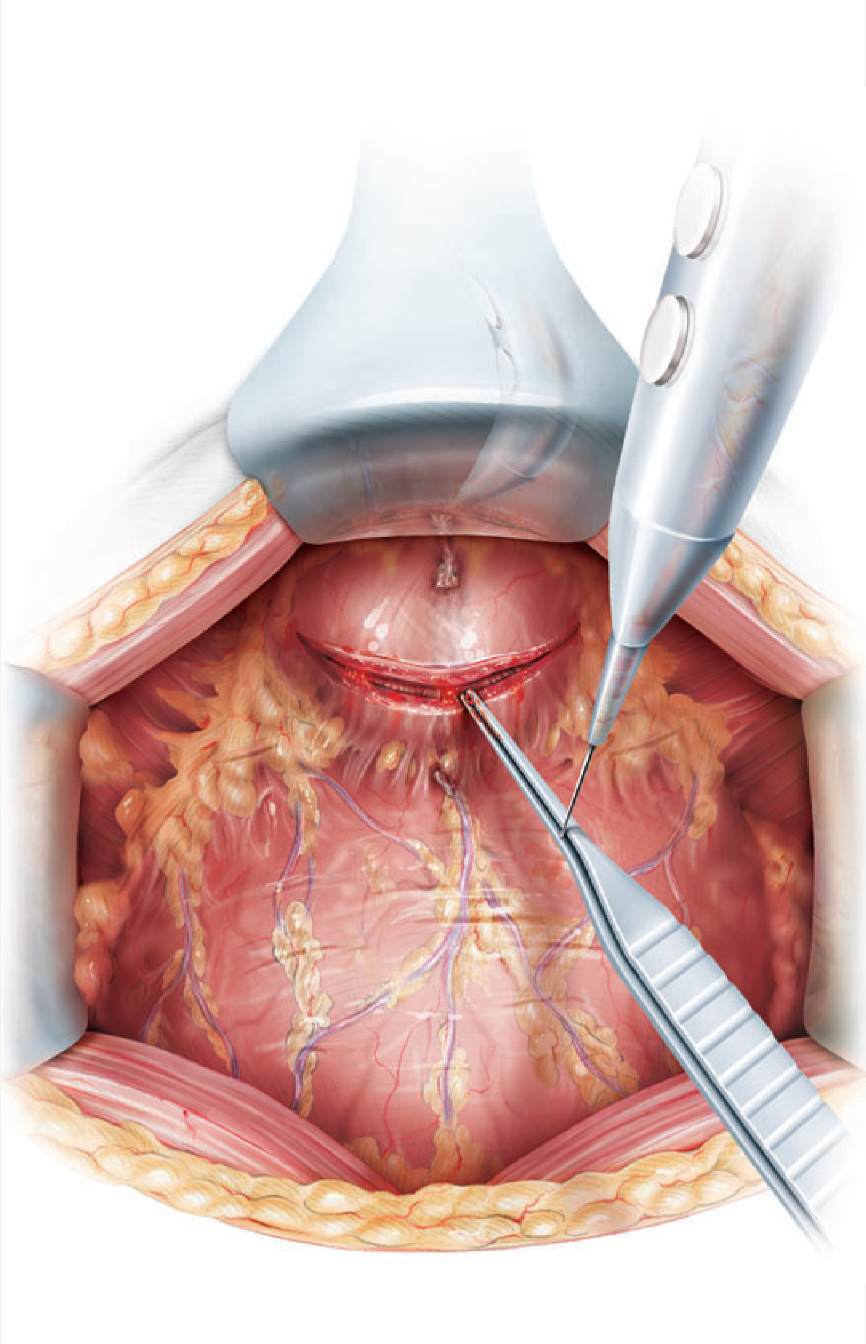

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Figure 4

The prostatic adenoma will then be visible, and a plane between this and the capsule can then be opened up using a Metzenbaum scissors. The urologist will not experience any difficulty in finding this plane.

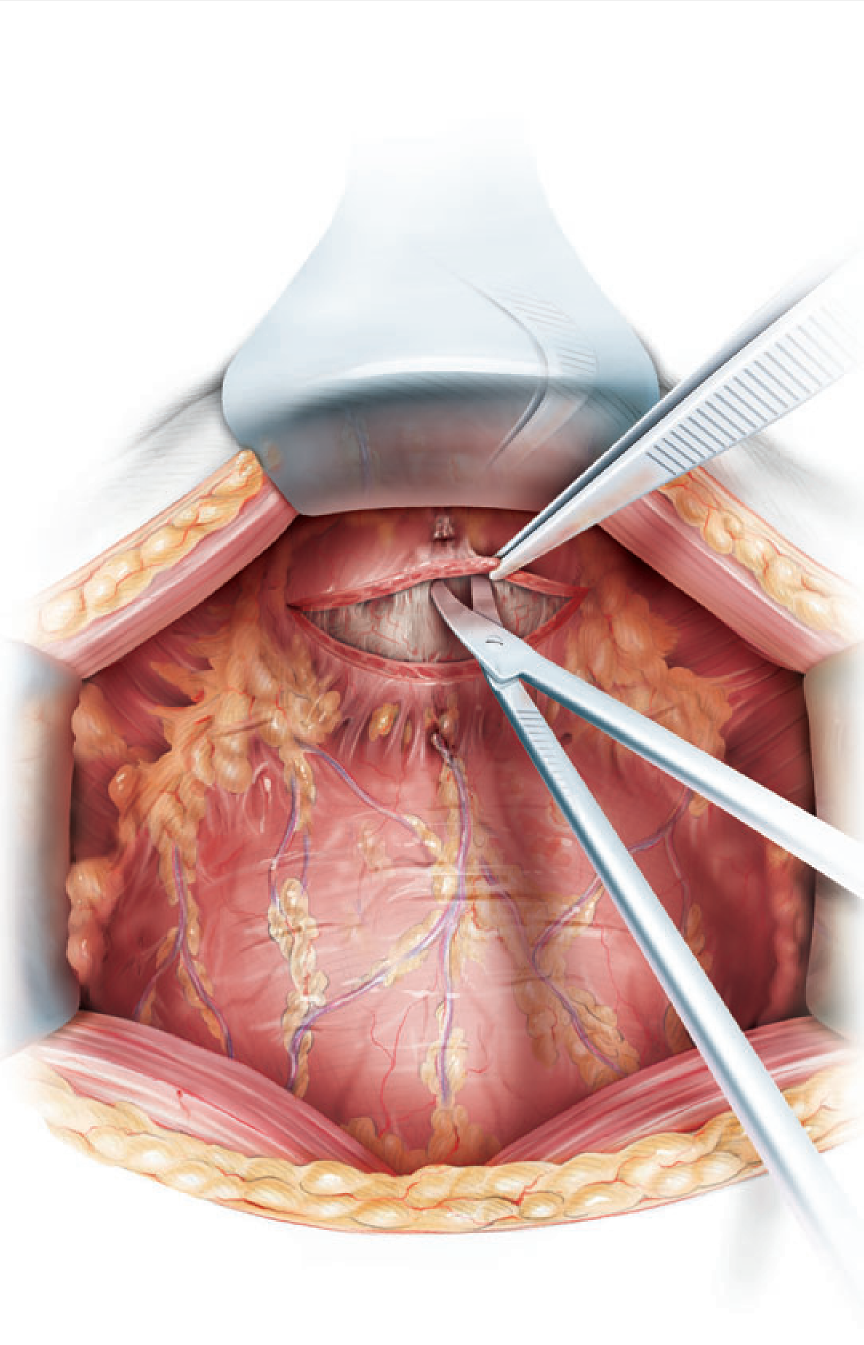

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Figure 5

The index finger should then be inserted into this plane, which can be further developed by sweeping the finger from side to side and then posteriorly.

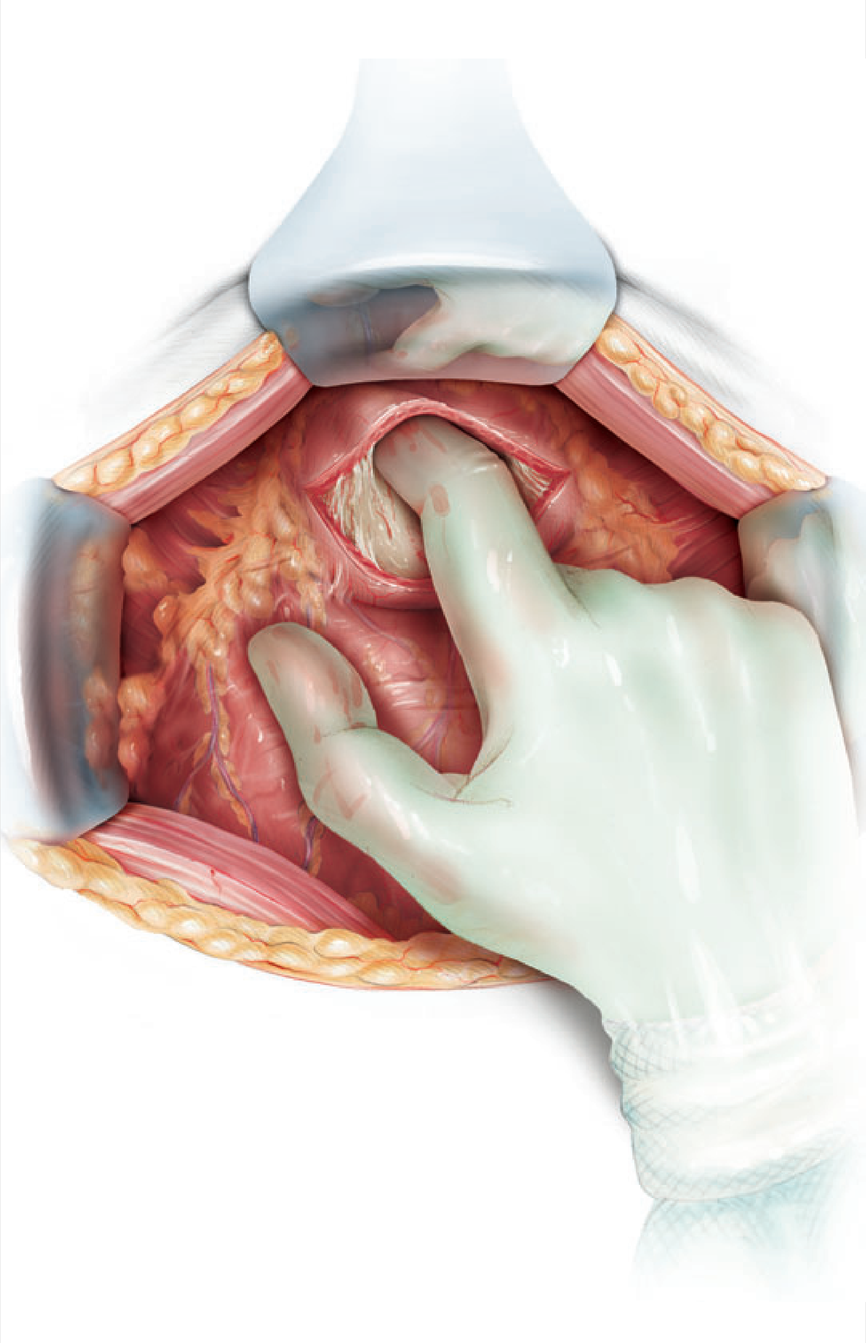

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Figure 6

Sometimes adhesions between the adenoma and the capsule must be cut with a scissors under direct vision.

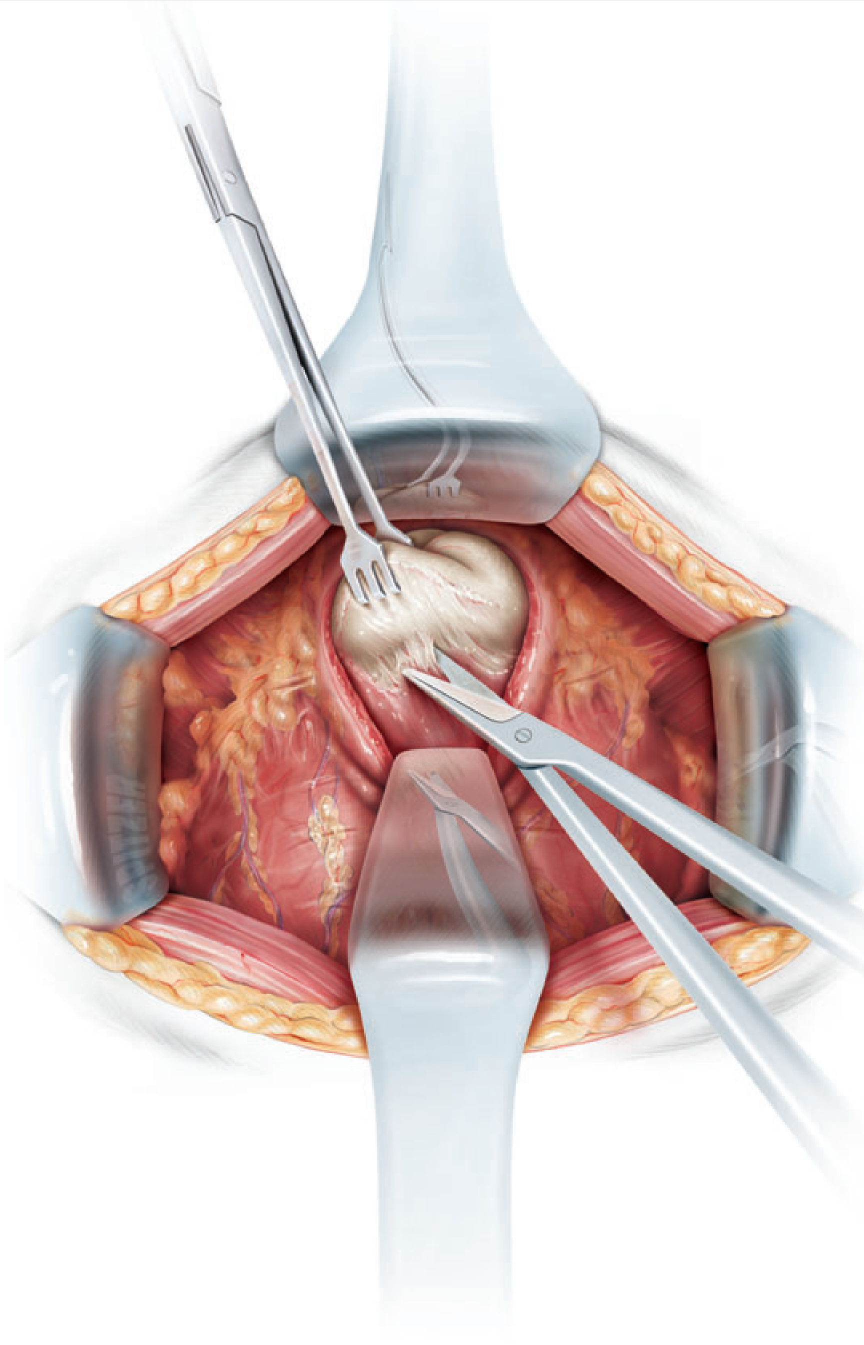

Figure 7

The urethra is then cut distally with the scissors. It is then lifted out of the prostatic cavity and the presence of any significant enlargement of the middle lobe established. The adenoma is then removed after separation from any bladder neck fibres. If there is any excess trigone, this should be excised and the trigone should then be sutured to the posterior capsule with 3/0 polyglycolic acid suture. If there are bleeding points within the prostatic cavity, these should be diathermised.

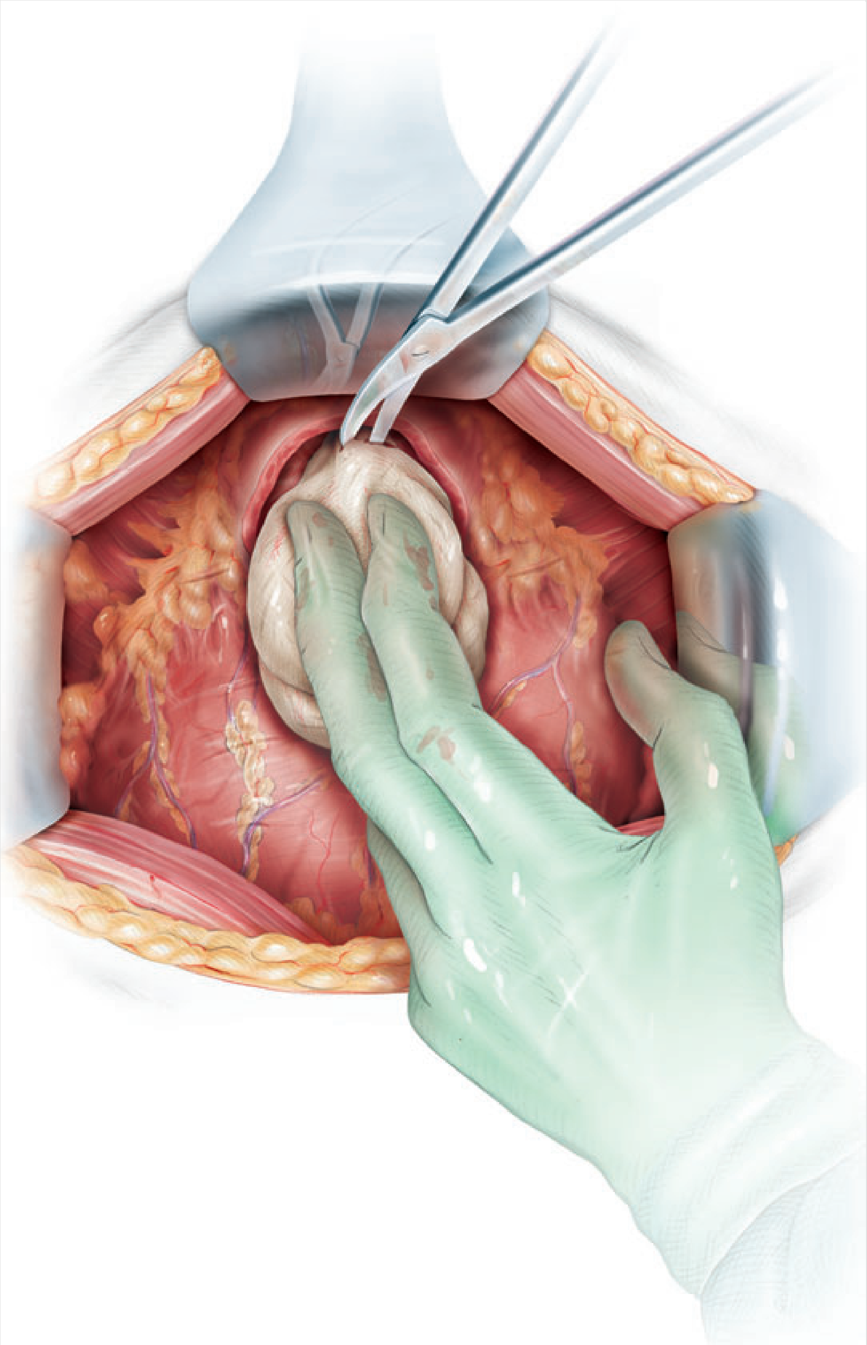

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Figure 8

A figure-of-eight suture, using O polyglycolic acid suture is inserted in the manner shown. One should be inserted at either end of the capsular incision and should include the bladder neck.

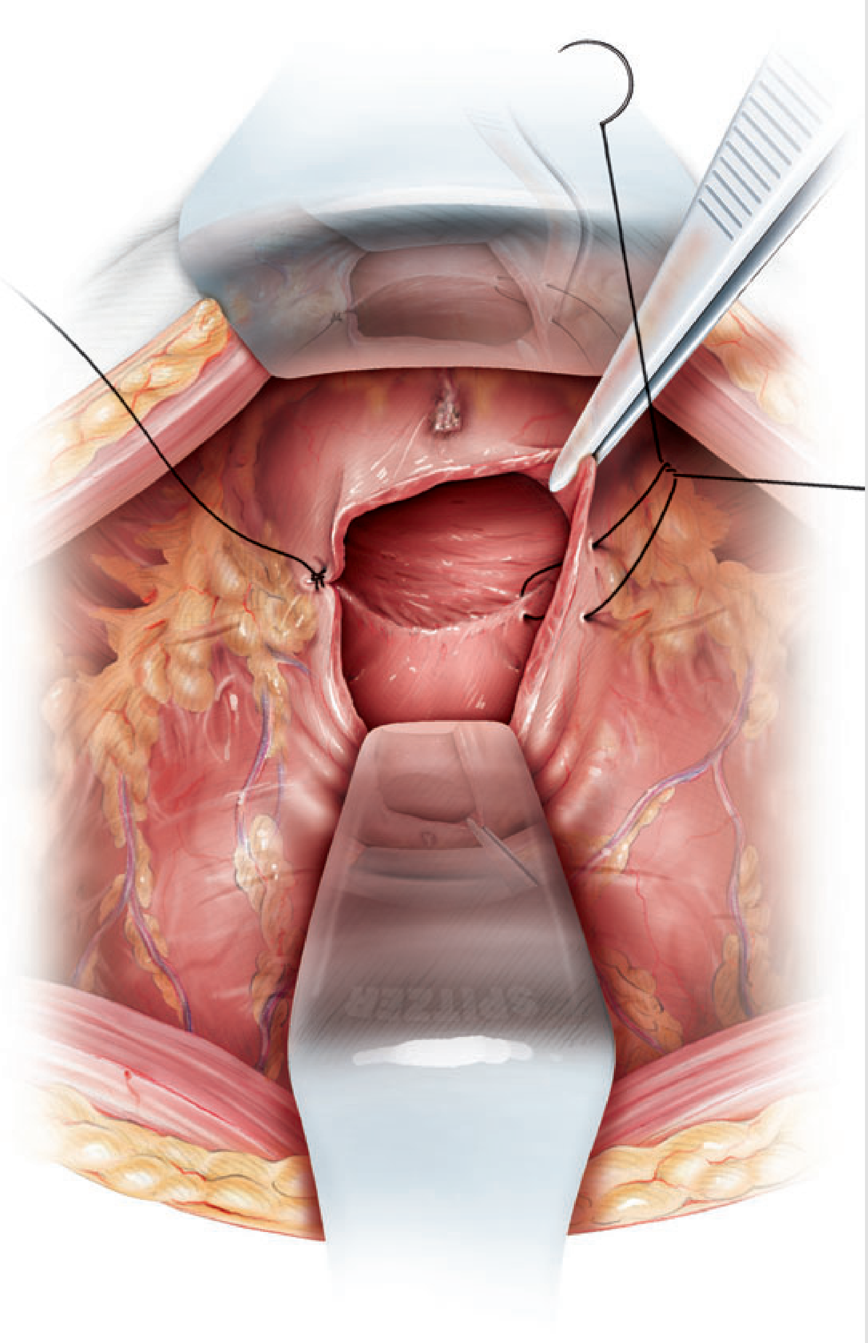
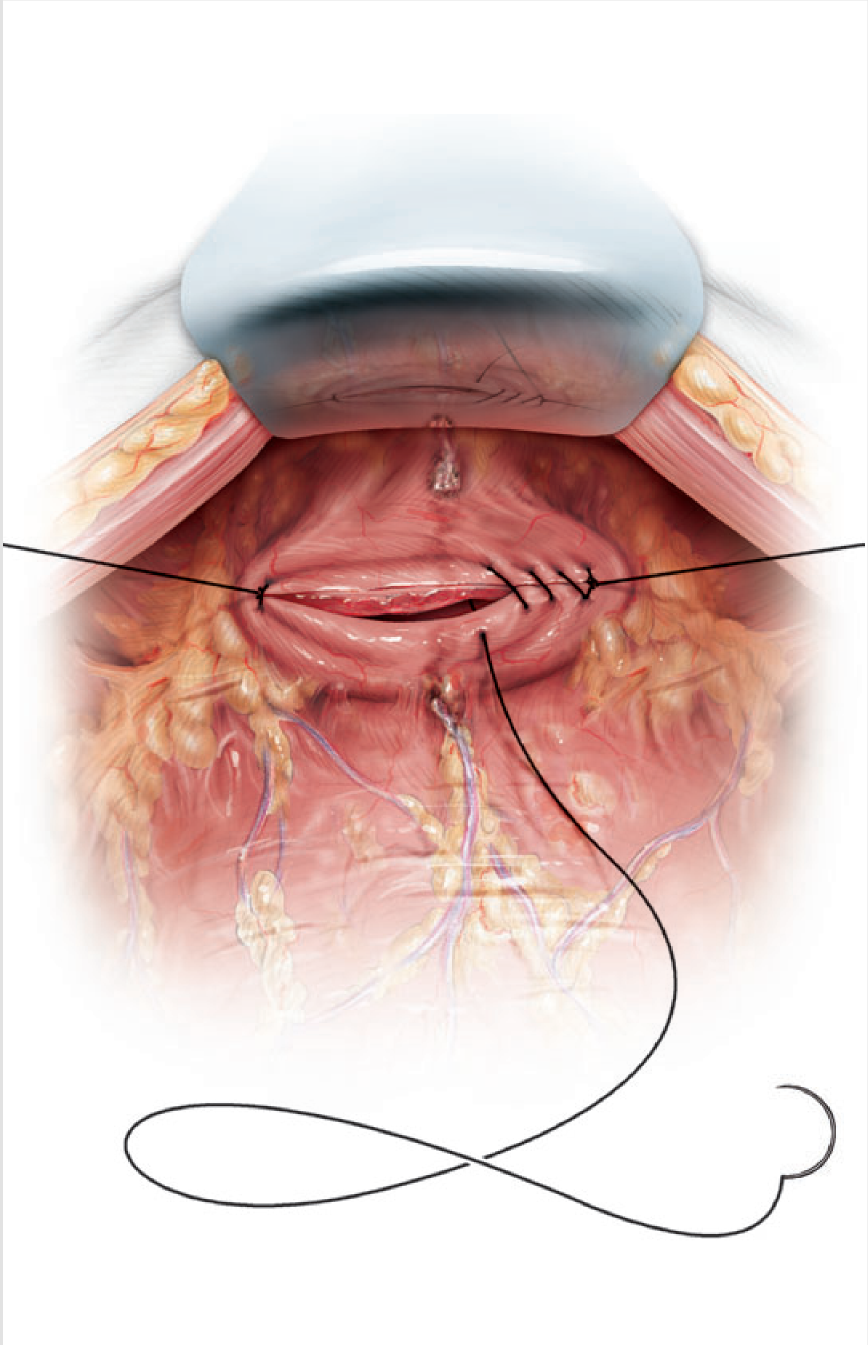


Figure 9

One of these is then run continuously across the capsule to the opposite suture, to which it is tied.

A size 22 Foley Haematiana artheat is inserted into the bladder and 30ml of fluid first filled into the balloon. A Robinson drain is used to drain the retropubic space. The wound is then closed. The catheter may be left in the bladder for 3 to 4 days and removed before the patient leaves hospital on the fifth post-operative day.



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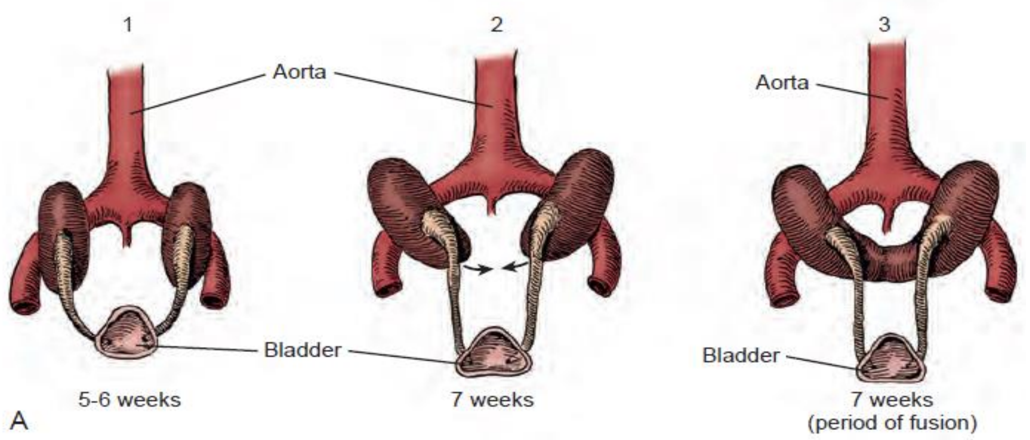
Paediatric Urology

1) Horse shoe kidney embryology and management of bilateral staghorn in a horse shoe kidney.

The horseshoe kidney is the **most common** of all renal fusion anomalies. Horseshoe kidney occurs in 0.25% of the population, or about 1 in 400 persons with a male-to-female ratio of 2: 1.

Embryology:
The abnormality occurs between **4 and 6 weeks of gestation**, after the ureteric bud has entered the renal blastema. In view of the ultimate spatial configuration of the horseshoe kidney, the entrance of the ureteric bud occurred before rotation and before renal ascent. The horse shoe kidney occurs due to median fusion of metanephric tissue during early gestation. Subsequent entrapment of the fused lower pole below the inferior mesenteric artery results in an incomplete cephalad migration and associated malrotation.



Recent animal models suggest role of **notochord and sonic hedgehog gene (SHH)** signal in the development of HSK. The notochord is *not* necessary for nephrogenesis but *is required* for correct positioning of the metanephric kidney, whereas the axial SHH signal is critical for kidney positioning along the mediolateral axis. Studies provide insights into the molecular basis for horseshoe kidney formation and provide an explanation for the increased incidence of horseshoe kidneys in children with vertebral and neural tube defects.

Description:

- In 95% of cases, the kidneys join at the **lower pole**, which occurs before the kidneys have rotated on their long axes.
- The pelves and ureters of the horseshoe kidney are usually anteriorly placed, crossing ventrally to the isthmus.
- The isthmus is generally bulky and consists of parenchymatous tissue with its own blood supply. Occasionally it is just a flimsy midline structure composed of fibrous tissue that tends to draw the renal masses close together. The isthmus is located adjacent to the **L3 or L4 vertebra** just below the origin of the inferior mesenteric artery from the aorta.

.

- The calyces are **normal in number and are atypical in orientation**. Because the kidney fails to rotate, the calyces point posteriorly, and the axis of each pelvis remains in the vertical or obliquely lateral plane (on a line drawn from the lower to the upper poles).

- The lowermost calyces extend caudally or even medially to drain the isthmus and may overlie the vertebral column.
- The uteropelvic junction (UPJ) is commonly deformed owing to the **high insertion** of the ureter into a typically elongated renal pelvis.
- The course of the proximal ureter is similarly aberrant; it drapes ventrally over the isthmus, where it may be compressed by vessels supplying the lower pole and isthmus.
- Ureteral obstruction that may result from these anomalies can give rise to hydronephrosis, urinary stasis, sepsis, and calculi formation **in 20 %(up to 80%)** of patients. Hypovolemia, hypercalciuria, and hypocitraturia are the most common metabolic defects.

Management of bilateral staghorn calculus in HSK:
Depending on the presentation, staghorn calculus in a HSK may have been detected using plain XRAY KUB done for symptoms or ultrasound KUB.
Preoperative cross sectional imaging using CT scan is recommended to delineate exact anatomy, aberrant vessels and location of the surrounding structures such as the colon.

The management of bilateral staghorn calculi in a HSK is challenging.
The options include:

a) Single stage bilateral open pyelolithotomy
b) Staged open pyelolithotomy
c) Staged PCNL

The patient should be consented for staged procedures, multiple procedures, incomplete stone clearance and need for auxillary procedures.

In considering PCNL in a horseshoe kidney, the characteristic lower and centrally oriented position of the kidney, the orientation of the collecting system, and the abnormal blood supply should be taken into account.

- In horseshoe kidneys the cephalad the vasculature has little variation; however, more caudally the renal vasculature varies considerably. Therefore, a puncture of the dorsal or dorsolateral aspect of the kidney will be well away from major renal vessels.
- The lower poles calyces lay within a coronal plane, angled medially, and are seldom suitable for direct puncture. However, the upper pole calyces are more posterior and lateral and are often subcostal, providing a convenient and relatively safe route for PNL access.
- The standard site for PNL (inside the posterior axillary line just caudad to the 12th rib) is punctured, but the angle of the puncture is caudad rather than cephalad. Because most of the calyces of horseshoe kidneys point either dorsomedially or dorsolaterally, they are **more favorably positioned for puncture than in normal renal units**.
- Because of the malrotation of the kidney, the renal pelvis may be more anteriorly located and the **length of the nephrostomy tract often exceeds the length of the rigid nephroscope, necessitating the use of flexible nephroscopy or multiple accesses**.
- Flexible nephroscopy also may be required to gain access to the lower medial calyces, where stones are often found.

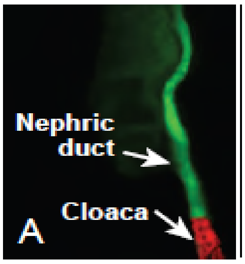
- Should a simultaneous bilateral approach be selected the second side should be pursued only if no significant bleeding is encountered on the first side, the first side did not take an undue amount of time, the patient is clinically stable, and the anesthesia team is agreeable.

2) Embryology of ectopic ureter

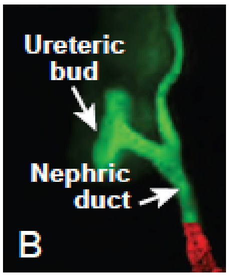
- An ectopic ureter is any ureter, single or duplex, that does **not enter the trigonal area of the bladder**. In a duplex system this is inevitably the upper pole ureter, presumably because of its budding from the mesonephric duct **later** than the lower pole with later incorporation into the developing urogenital sinus.
- The pathogenesis of ureteral ectopia with or without ureterocele results in renal maldevelopment caused by defective ureterotrigonal connections.
- This involves the **common nephric duct (CND), ureteral budding, ureterometanephric interactions, and bladder and trigone development**.
- Ectopic ureters can arise due to **abnormal timing or location** of the primary ureteral budding from the mesonephric ducts, or abnormalities at the **any stage** of ureter interacting with bladder.

Normal development: (these events occur between 9 weeks – 14 weeks of gestation)

1) Nephric duct (Mesonephric duct/ Wolffian duct) insertion into cloaca

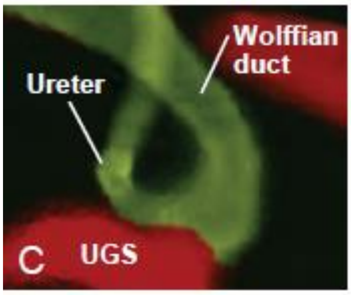


2) Ureteric bud formation

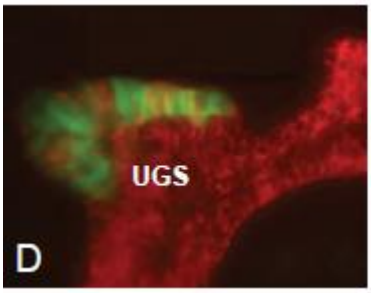


Common nephric duct (CND) – part of nephric duct distal to ureteric bud formation

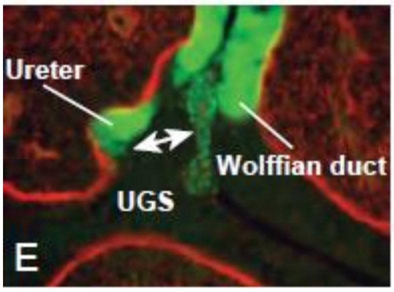
3) Apoptosis of CND with loop interpositioning of new ureteric orifice



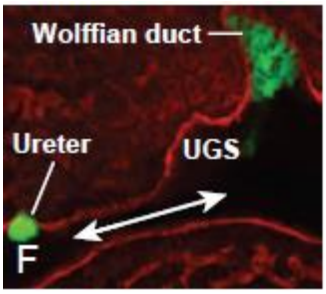
4) Intercalation – Ureteric bud and bladder interaction

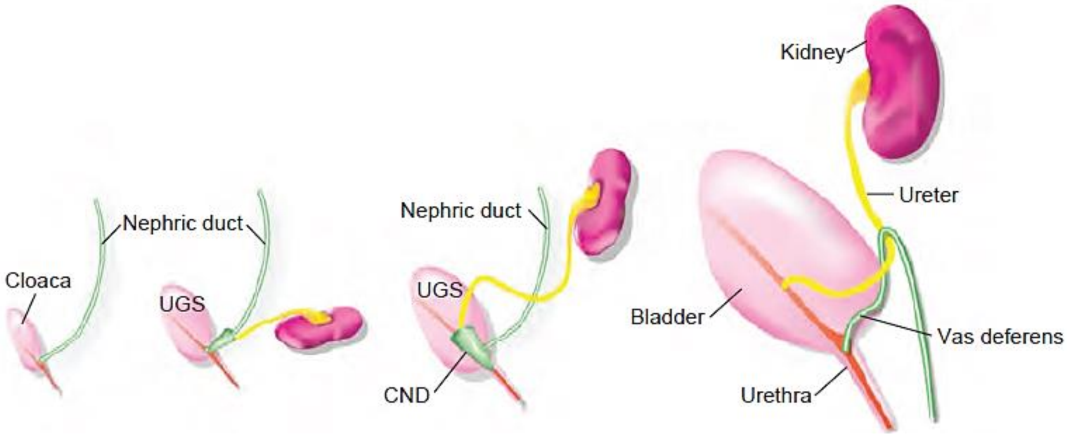


5) Second wave of apoptosis of distal ureter and CND



6) Expansion and elongation of the bladder has moved the ureter orifice farther away from the mesonephric (wolffian) duct

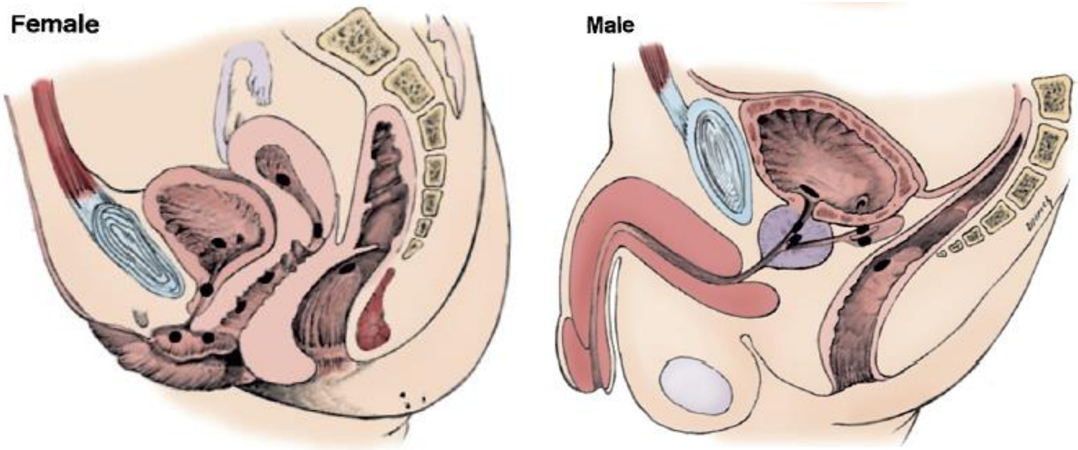




To summarize, any of the stages of the above normal development (**timing/location/interaction**) can lead to ectopic ureter.

Other points:

- In contrast to the classic model in which the CND (**mesoderm**) forms the trigone, the revised model includes regression of the CND in the normal animal through apoptosis and formation of the trigone from the **endoderm**, like the bladder.
- Because the ureteral bud derives from the wolffian duct, the ectopic ureter will not insert directly into the müllerian structures (vagina, cervix, uterus), but will be associated with them through the remnant of the wolffian duct, the Gartner duct, that runs alongside the mature müllerian structures (can even insert into rectum in both male and female – mechanism unclear)
- Given that the wolffian duct in the male is never associated with any structures below the pelvic floor and sphincter, **males do not present with urinary incontinence**, as is seen in females.



Lastly, the **Weigert-Meyer rule** describes the inverse relationship of the duplex ureteral orifices, in which the ectopic ureter or ureterocele associated with the **upper pole is caudal and medial to the lower pole ureteral orifice**.

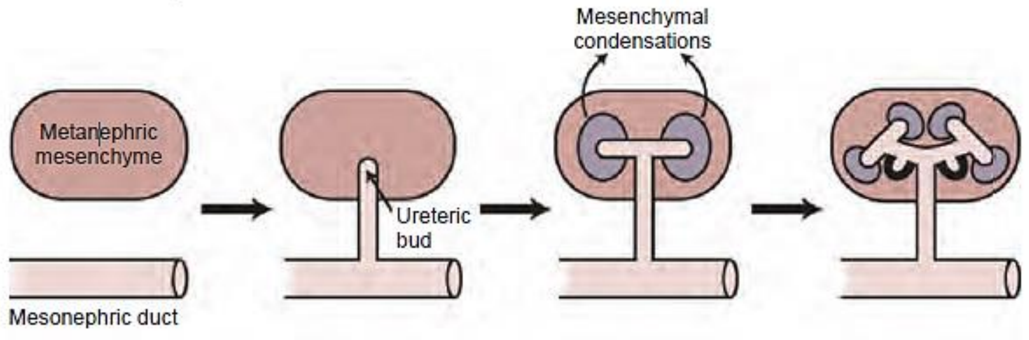
3) Define Renal agenesis, Dyplastic Kidney, Hypoplastic Kidney, Cystic Dysplastic kidney and multicystic dysplastic kidney with diagrams

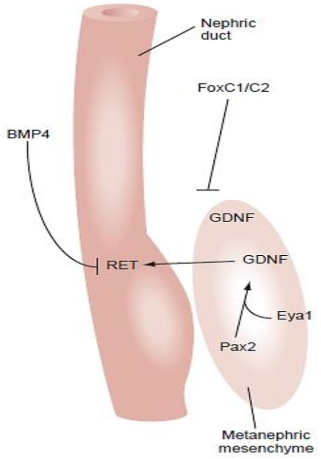
A) Renal agenesis

- **Complete absence** of unilateral (unilateral renal agenesis) or bilateral (bilateral renal agenesis) is called renal agenesis.
- Normal kidney develops from **metanephric blastema** (specialized condensed part of metanephric mesenchyme which is a part of intermediate mesoderm).
- Further development occurs due to **reciprocal interaction between ureteric buds** (from distal part mesonephric duct/Wolffian ducts) and metanephric blastema. This interaction occurs around **28th day** of gestation.

So normal kidney development requires:

- **a)** Normal metanephric blastema formation
- **b)** Normal signal from metanephric blasema to Wolffian duct which leads to ureteric bud formation
- **c)** Normal reciprocal interaction between ureteric bud and metanephric blastema





Inductive interactions during early kidney development. Glial cell line–derived neurotrophic factor (GDNF) is secreted from the metanephric mesenchyme and activates the RET receptor tyrosine kinase in the ureteric bud epithelium. The expression and localization of GDNF are positively regulated by Eya1 and Pax2 and negatively by FoxC transcription factors. The inducibility of nephric ducts to GDNF signaling is restricted by the action of bone morphogenetic protein-4 (BMP4). (Modified from Dressler GR. Tubulogenesis in the developing mammalian kidney. Trends Cell Biol 2002;12:390–5.)

Abnormalities at any of the above levels can lead to renal agenesis.

B) Dyplastic kidney and hypoplastic kidney:

Renal **dysgenesis** is defined as **maldevelopment** of the kidney that affects its **size, shape or structure**. Renal dysgenesis is of two types – Renal dyplasia and renal hypoplasia.

Renal dysplasia - “Dysplasia” literally means “abnormal tissue”.

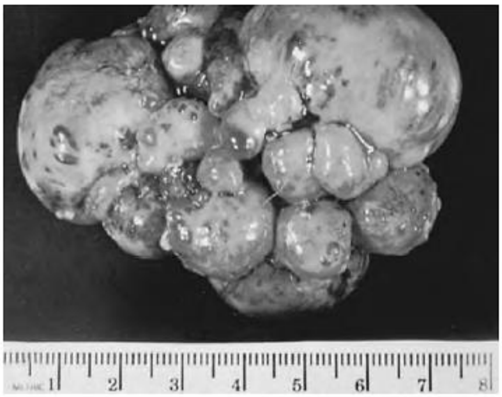
- Truly, dysplasia is a histo-pathological diagnosis. It is characterised by presence of embryonic, immature mesenchyme, and primitive renal components.
- The hallmark of dysplasia is the **primitive duct**, a duct encircled by a collar of fibromuscular cells.
- Renal dysplasia is the primary cause of childhood end-stage renal disease (ESRD), and two main theories have been considered in its pathogenesis:
  (1) A primary failure of ureteric bud activity and
  (2) A disruption in renal development produced by fetal urinary outflow impairment (obstruction)

Renal hypoplasia is another form of renal dysgenesis, which is defined as the **underdevelopment of a tissue** or organ and which is usually caused by a **deficiency in the number of cells**.

- Renal hypoplasia is a condition in which there is a reduction in the size of the functioning renal mass. Use of the term *hypoplasia* should be restricted to kidneys that have less than the normal number of calyces and nephrons but are **not dysplastic or embryonic**.
- These are kidneys that are **morphologically normal but have either a reduced number of nephrons or smaller nephrons.**

C) Multicystic dysplastic kidney disease

- MCDK is a developmental anomaly resulting in **multiple cysts of varying sizes, without identifiable normal renal parenchyma**. These kidneys have no function by definition, and usually the contralateral kidney is normal and exhibits compensatory hypertrophy.
- Only unilateral involvement is compatible with life. The kidney often **does not have a reniform appearance, and it is typically associated with an atretic ureter** with no connection between glomerulus and calyces.
- Typically, the kidney has the appearance of a **bunch of grapes, with little stroma between the cysts**.
- MCDK is the most **common type of cystic disease** and **second most common cause of abdominal mass** in **infants**.



A typical multicystic dysplastic kidney having the appearance of a bunch of grapes. The kidney is composed almost entirely of cysts with very little stroma.

- "**Bunch of grapes**" with no normal renal parenchyma in between with **no reniform shape**
- Cysts are of **varying sizes** in haphazard distribution.
- No central/medial cyst. **No visible communication** between cysts (cf: hydronephrosis)

4) Medullary sponge kidney

- Medullary sponge kidney (MSK; also known as *precalyceal canalicular ectasia)* **is characterized by tubular dilation of the distal portion of the collecting ducts with numerous associated cysts and diverticula strictly confined to the medullary pyramids.**
- These dilated ducts have the appearance of the **bristles on a brush** and often are more ectatic and filled with calcifications, giving an appearance suggestive of a **bouquet of flowers.**
- **Incidence: 1 in 200 IVUs** (among all indications for IVU). Among stone formers : 2.1% to 21%
- It is usually regarded as a **nonhereditary** disease

Clinical features

MSK is usually a **benign** process, and it may remain asymptomatic and undetected for life. Clinical presentation usually occurs after age 20 years. It is commoner in **females**.

- **Renal colic – most common** (50% to 60%)
- Urinary tract infection (20% to 33%)
- Gross hematuria (10% to 18%).
- **One third to one half of the patients with MSK have hypercalciuria**
- Incomplete distal renal tubular acidosis – seen in 30% to 40%
- In the absence of infection, the stones passed by patients with MSK are composed of **calcium oxalate**, either alone or in **combination with calcium phosphate.**

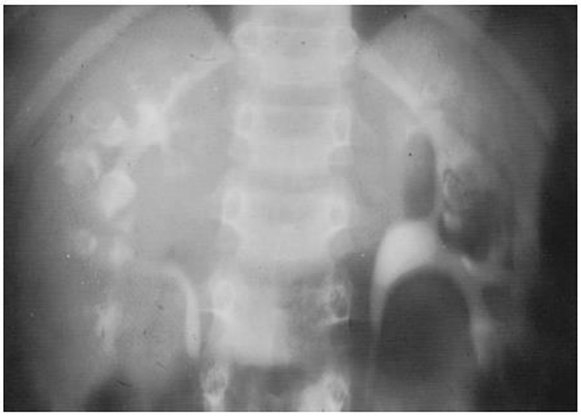
- MSK has also been reported in association with rare congenital anomalies, such as hemihypertrophy, Beckwith-Wiedemann syndrome (macroglossia, omphalocele, and gigantism), Ehler-Danlos syndrome, anodontia, and Caroli disease.

Histopathology

- The principal finding is dilated intrapapillary collecting ducts and small medullary cysts, which range in diameter from 1 to 8 mm and give the cross-sectioned kidney the **appearance of a sponge.**
- The renal size is usually **normal or slightly enlarged**.
- Themprecalyceal canalicular ectasia may involve one or more renal papillae in one or both kidneys. The lesions are bilateral in 70% of cases

Diagnosis

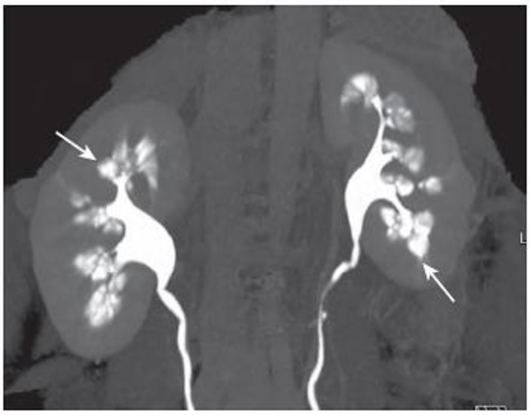
In general, classic intravenous urography is more sensitive than CT in detecting mild cases of MSK; however, three-dimensional (3D) volume-rendered imaging acquired during the urographic phase of a multidetector CT urogram can also establish the diagnosis.



Characteristic puddling of contrast medium in the ectatic papillary collecting ducts makes the diagnosis of medullary sponge kidney.

Urographic features of MSK

1) Enlarged kidneys, sometimes with calcification, particularly in the papillae
2) Elongated **papillary tubules or cavities that fill with contrast medium**
3) **Papillary contrast blush**
4) Persistent medullary opacification
5) Calcium deposits within the tubules may appear as renal calculi or **nephrocalcinosis**



Contrast-enhanced maximum intensity projection three-dimensional image from multidetector-row computed tomography (CT) urogram shows characteristic papillary blush *(arrows)* associated with scattered calculi within the dilated collecting tubules. The CT demonstration is equivalent to the well-documented intravenous pyelography findings.

Treatment

It is the complications of MSK, calculus formation, and infection that require management.

- **Potassium citrate** – for hypercalciura and hypocitraturia
- Liberal fluid intake, low sodium diet
- **Thiazides** – for hypercalciuria (Thiazides should be prescribed for stone formers even in the absence of hypercalciuria
- Treat UTIs – **long term prophylaxis** may be needed
- For stones – ESWL and PCNL may be used if large

5) Bilateral single ectopic ureters – clinical features and management

I. Epidemiology

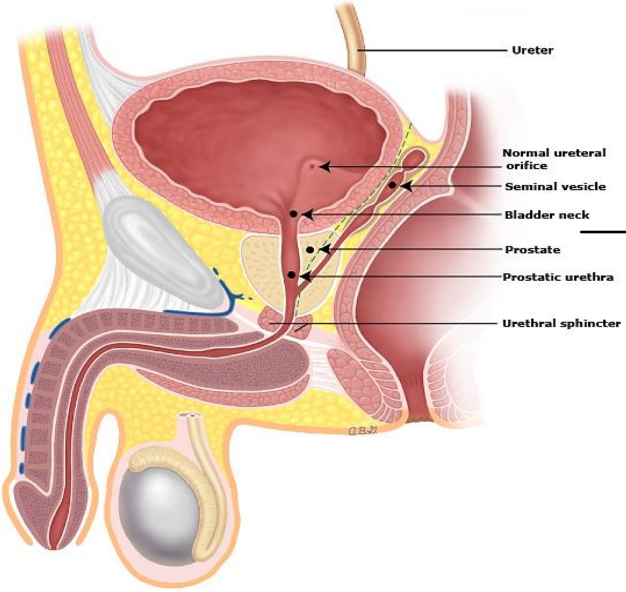
- Incidence: 1:1900 in autopsy series
- Male: Female = 1:6
- Bilateral: 10%

II. Single versus duplex system

- Western literature: 75-90% ectopic ureters associated with duplex kidney
- India and Japan: about 75% associated with single kidney system

III. Ureteric orifice opening

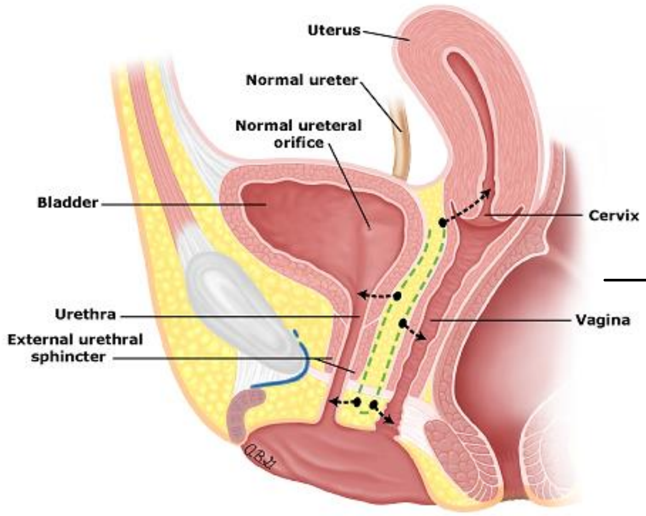
The ectopic orifice is always found along the pathway of the developing mesonephric system.



Male

- Posterior urethra (MC – 50%)
- Seminal vesicles (33%)
- Vas deferens
- Bladder neck
- Prostate
- Ejaculatory duct orifice to epididymis

Above external sphincter so no incontinence



Females

- Bladder neck and upper urethra – 33%
- Vaginal vestibule between the urethra and vaginal opening – 33 %
- Vagina – 25 %
- Cervix and uterus – <5%

Only girls with a ureteral orifice site at or above the bladder neck and upper urethra will be continent.

(Green dotted lines in both above diagrams are other pote

IV. Clinical presentation

Prenatal presentation — Ectopic ureter is increasingly being diagnosed by antenatal ultrasonography. In these cases, hydronephrosis is the usual presenting finding, most likely due to obstructed flow from narrowing of the ureter or bladder neck obstruction as the ectopic ureter passes through the muscle of the genitourinary diaphragm.

Postnatal presentation — Ectopic ureters present differently in toilet-trained males and females, primarily because in two-thirds of affected females, they bypass the external sphincter, resulting in incontinence, whereas the orifice of ectopic ureters in males is always proximal to the urinary sphincter.

Male — in males, an ectopic ureter is usually detected during an evaluation for anatomic abnormalities following a urinary tract infection (UTI). Rarely, if the ureter enters the genital ducts, patients may present with epididymoorchitis. Males never present with incontinence because the ectopic ureter is always proximal to the external urethral sphincter.

Other presentations for boys with ectopic ureters include:

- Flank pain
- Sense of urgency or frequency in patients with ureteric termination in the posterior urethra
- In rare cases, newborn males with bladder outlet obstruction due to a dilated prostatic ectopic ureter

Females — in infancy, girls usually present with UTI. However, after toilet training, girls generally present with incontinence because, in most cases, the site of insertion of the ectopic ureter is distal to or bypasses the external sphincter, usually ending in the vaginal vestibule or vagina. The parents typically report that the girl has normal voiding habits (**in the rare case where bilateral ectopic openings are below the sphincter the girl may have continuous incontinence**), but is always wet. She may become wetter when she is sitting on the parent's lap because of urine pooling in the dilated ureter or vagina. Some older girls may present with pyelonephritis, which more likely occurs in patients with a dysplastic kidney and dilated ectopic ureter. Infection results from urinary stasis and obstruction. In addition, girls may present with flank pain.

Other anomalies

Genitourinary	Non genitourinary
Renal hypoplasia/dysplasia – most common Renal agenesis	Anorectal malformation
Urethral duplication	Tracheoesophageal fistula
Hypospadias	Congenital cardiac lesions
Cloacal abnormalities	Conductive hearing loss
Undescended testes	Spinal cord lesions including meningomyelocele
Ureterovaginal duplication Mullerian abnormalities – uterine didelphys/vaginal duplication	

V. Diagnosis and Evaluation

Diagnostic tests

a) Renal ultrasound

b) IVU

c) CT/MRI – If ultrasound and IVU are not conclusive and clinical suspicion exists – in these cases cross sectional imaging will pinpoint location of the ureter and the site of drainage

d) Voiding cytsourethrogram (VCUG)

e) Renal scan – DMSA for renal function assessment

f) Endoscopic assessment of the lower urinary tract

VI. Management

Goals:

- Preservation of renal function
- Elimination of infection
- Relief of obstruction and reflux
- Maintenance of urinary continence

Single system — In patients with bilateral ectopic ureter in a single system, this is achieved by a combination of nephroureterctomy/observation of poorly functioning side and distal ectopic ureteric excision and reimplantation of the better functioning side.

OUTCOME — in children with ectopic ureters, long-term surgical outcome is excellent, with resolution of incontinence in almost all affected patients, and decreased rates of urinary tract infection (UTI).

However, patients with either bladder outlet obstruction or **bilateral single-system** ectopic ureter may have voiding dysfunction and/or small bladders with inadequate capacity. These patients are less likely to achieve continence. In some cases, bladder augmentation has to be performed**.**

6) Prune Belly Syndrome (=Eagle Barett syndrome =triad syndrome=abdominal musculation syndrome)

PBS represents a constellation of anomalies of varying degree – the major findings are a triad of **defeciency in abdominal musculature, bilateral intra-abdominal testes and anomalous urinary tract**. (cf: Pseudoprune – descended testes)

I. **Incidence**: 1 in 29,000 to 1in 40,000 live births. **95% occurs in males.**

II. **Genetics and embryology:**

Most cases are sporadic with normal karyotype. Has been associated with Turner syndrome and trisomy syndromes (trisomy 13 and 18)

Embryology – Changes at **third week** of gestation

Proposed theories

a. Early in utero urethal obstruction

b. Primary defect in lateral plate mesoderm

c. Intrinsic defect in urinary tract leading to ureteral dilation and fetal ascites

d. Yolk sac defect

III. **Clinical features**

Genitourinary abnormalities

Organ	**Features**	**Comment**
Kidney and ureter	Renal dysplasia – 50% Non obstructive hydronephrosis VUR – 75%	Calyceal morphology preserved Abnormal ureteral musculature
Bladder	Massively enlarged with pseudodiverticulum at urachus Patent urachus in 25-30%	Bladder has increases collagen to muscle ration in the absence of obstruction (wall is smooth) Large capacity bladder (**50% still void spontaneously**)
Prostate and accessory sex organs	Prostatic hypoplasia with dilation of posterior urethra Atretic vas and seminal vesicles	Retrograde ejaculation because of incompetent bladder neck
Anterior urethra	Urethral atresia and megalourethra	Unless associated with patent urachus urethral atresia is often lethal Megalourethra – fusiform/scaphoid
Testes	Bilateral UDT – MC overlying iliac vessels	Pseudoprune – descended testes

Extragenitourinary abnormalities

Organ	**Features**	**Comment**
Abdominal wall defect	**Inferior and medial segments affected most**	One of the triads
Cardiac	Patent ductus arteriosus VSD, ASD, TOF	10 % cases
Pulmonary	Pulomonary hypoplasia due to severe oligohydramnios.In addition pneumothorax and pneumomediastinum	55% of PBS survivors
Gastrointestinal	Abnormal mesenteric fixation, splenic torsion Acquired megacolon	30% cases
Orthopaedics	Compression effect due to oligohydramnios – dimpling of lateral knee	30-45%

IV. Presentation

a) Prenatal diagnosis and management

- Bilateral HDUN suggestive of bladder outlet obstruction (USG)
- D/d – PUV, megacystits megaureter syndrome
- Difficult to reliably diagnose on antenatal USG even as late as 30 weeks
- Pregnancy termination only if severe degree of obstruction and severe oligohydramnios

b) **Neonatal** – classic wrinkled skin appearance of abdominal wall should prompt to look for other anomalies

c) Spectrum of the disease

Category	Characteristics	Comment
I	Renal dysplasia, oligohydramnios, pulmonary hypoplasia, Potter features, urethral atresia	**Severe** form High perinatal mortality Simple catheterisation is all that may be justifiable
II	Full triad features, minimal renal dysplasia, No pulmonary hypoplasia, may progress later to renal failure	
III	Incomplete/mild triad Mild to moderate uropathy No renal dysplasia/no pulmonary hypoplasia Stable renal function	**Most common** form Treatment reserved for recurrent UTI, VUR, upper tract deterioration

V. Evaluation and management

- **Multidisciplinary** approach is needed – neonatologist, nephrologist, urologist and other specialities such as cardiology.
- **VCUG** is indicated in the neonatal period if there is renal insufficiency or evidence of bladder outlet obstruction. It is to be done only after antibiotic prophylaxis.
- Chest radiography is necessary to evaluate pulmonary status.
- Baseline assessment of renal function and ultrasound to be done – baseline **serum creatinine <0.7mg/dl** is predictive of adequate renal function throughout childhood in the absence of recurrent UTIs.
- **Circumcision** is advisable to in the absence of structural penile abnormalities to reduce UTIs.
- Early intervention is indicated in the presence of bladder outlet obstruction – preferably **SPC** placement
- Other surgical interventions as appropriate include cutaneous vesicostomy, redction cystoplasty, urethral reconstruction, **orchiopexy (to be done at 6 months of age** – most likely prospect of single stage procedure)

- For abdominal wall reconstruction – various techniques such as Monfort-Ehlrich technique have been described. Abominal wall reconstruction has demonstrated improved bladder emptying, a more effective cough and improved defecation in addition to psychosocial benefits.

7) Management options in failed pyeloplasty

The success rates for open and minimally invasive (laparoscopic/robotic) pyeloplasties are between **90-100%.**

Factors for failure:

- Young age at initial surgery (less than 6 months)
- Prolonged urinary diversion (dry anastomosis)
- Missed anatomic findings (crossing vessel/longer ureteral segmen narrowing)
- Lack of retrograde pyelography
- Technical factors – anastomosis under tension/compromised vascularity

Treatment options for failed pyeloplasty (Salvage procedures for failed pyeloplasty)

1) Balloon dilation
2) Endopyelotomy – lower success rate - around 40% as salvage procedure.
3) Redo dismembered pyeloplasty – open/minimally invasive – may require transperitoneal approach – success rate approaching 80%
4) The various flap procedures depending on the anatomy
5) Ureterocalicostomy
6) If extensive ischemia and long stricture – may rarely need ileal replacement/autotransplantation with Boari flap pyelovesicostomy
7) If function of kidney is already compromised/ non reconstructable with normal contralateral kidney – nephrectomy

8) Antenatal hydronephrosis

Introduction – Prenatal diagnosis of urinary tract dilation (UTD) occurs in 1-2% of pregnancies.

Etiology

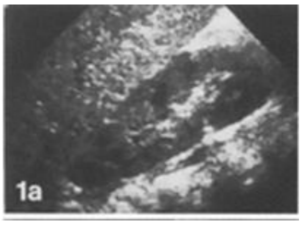
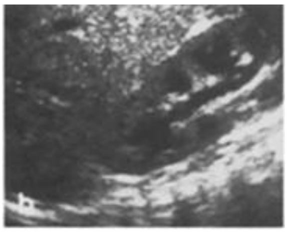
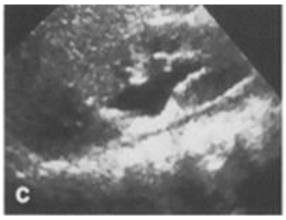
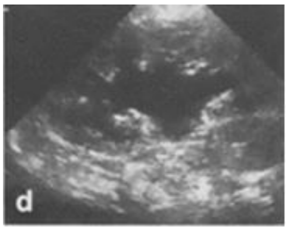
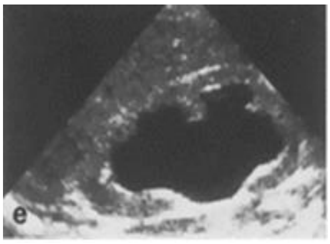
Etiology	**Incidence (%)**
Transient/physiologic	50–70
Ureteropelvic junction obstruction	10–30
Vesicoureteral reflux	10–40
Ureterovesical junction obstruction/megaureter	5–15
Multicystic dysplastic kidney disease	2–5
Posterior urethral valves	1–5

Ureterocele, ectopic ureter, duplex system, urethral atresia, Prune belly syndrome, polycystic kidney diseases, cysts	Uncommon

Society for fetal urology grading (SFU)

Till recently the SFU grading was most widely used for antenatal hydronephrosis with good consistency. To overcome its shortcomings (status of ureter, bladder, quality of renal parenchyma and oligohydramnios), UTD classification system is now used.

SFU grading

Grade	Description	Image (on coronal sonography)
0	Normal examination with no dilatation of the renal pelvis	
I	Mild dilatation of the renal pelvis only	
II	Moderate dilatation of the renal pelvis including a few calyces	
III	Dilatation of the renal pelvis with visualization of all the calyces, which are uniformly dilated, and normal renal parenchyma	
IV	Similar appearance of the renal pelvis and calyces as Grade III plus thinning of the renal parenchyma	

UTD classification system

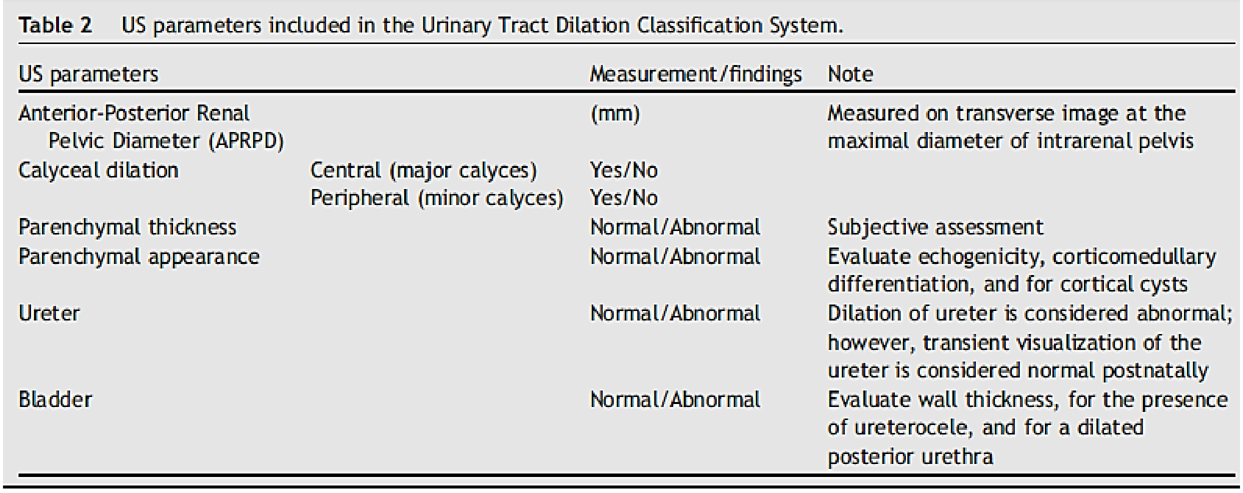


Table 2 US parameters included in the Urinary Tract Dilation Classification System.

US parameters		Measurement/findings	Note
Anterior-Posterior Renal Pelvic Diameter (APRPD)		(mm)	Measured on transverse image at the maximal diameter of intrarenal pelvis
Calyceal dilation	Central (major calyces)	Yes/No	
	Peripheral (minor calyces)	Yes/No	
Parenchymal thickness		Normal/Abnormal	Subjective assessment
Parenchymal appearance		Normal/Abnormal	Evaluate echogenicity, corticomedullary differentiation, and for cortical cysts
Ureter		Normal/Abnormal	Dilation of ureter is considered abnormal; however, transient visualization of the ureter is considered normal postnatally
Bladder		Normal/Abnormal	Evaluate wall thickness, for the presence of ureterocele, and for a dilated posterior urethra

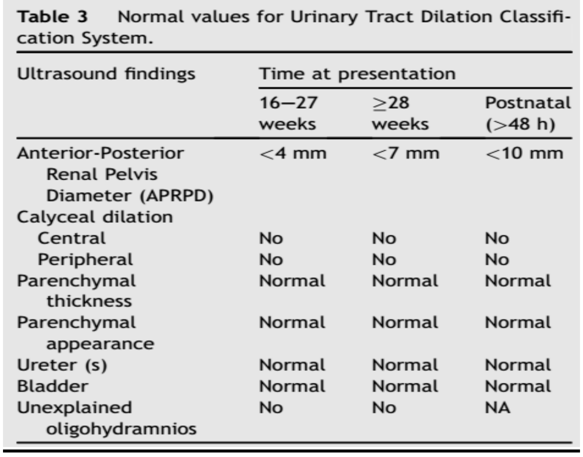
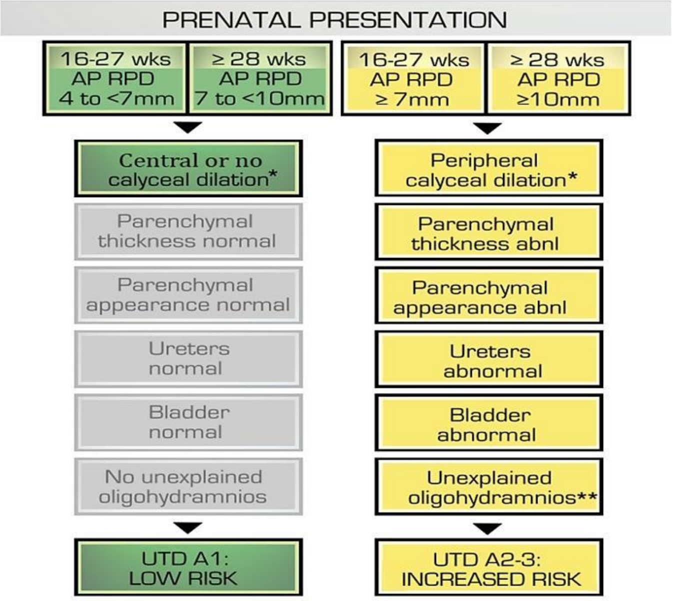


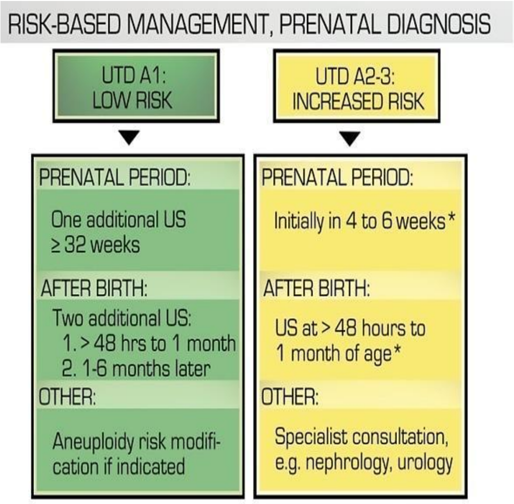
Table 3 Normal values for Urinary Tract Dilation Classification System.

Ultrasound findings	Time at presentation		
	16–27 weeks	≥28 weeks	Postnatal (>48 h)
Anterior-Posterior Renal Pelvis Diameter (APRPD)	<4 mm	<7 mm	<10 mm
Calyceal dilation			
Central	No	No	No
Peripheral	No	No	No
Parenchymal thickness	Normal	Normal	Normal
Parenchymal appearance	Normal	Normal	Normal
Ureter (s)	Normal	Normal	Normal
Bladder	Normal	Normal	Normal
Unexplained oligohydramnios	No	No	NA

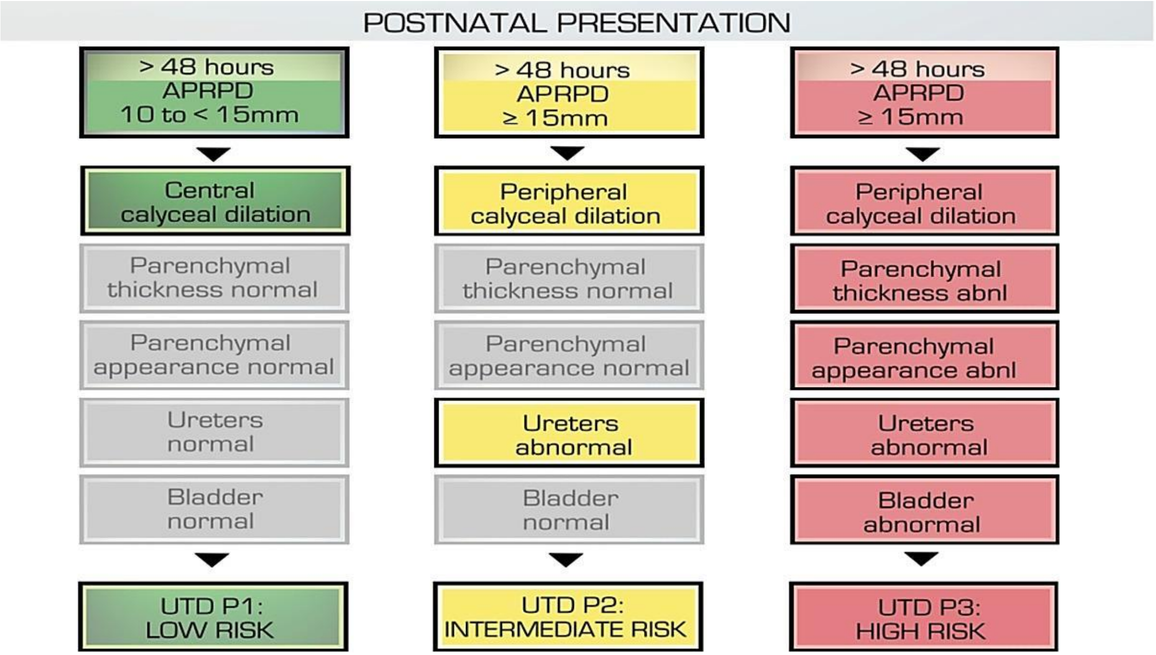

PRENATAL PRESENTATION
16-27 wks AP RPD 4 to <7mm
≥ 28 wks AP RPD 7 to <10mm
16-27 wks AP RPD ≥ 7mm
≥ 28 wks AP RPD ≥10mm
Central or no calyceal dilation*
Parenchymal thickness normal
Parenchymal appearance normal
Ureters normal
Bladder normal
No unexplained oligohydramnios
UTD A1: LOW RISK
Peripheral calyceal dilation*
Parenchymal thickness abnl
Parenchymal appearance abnl
Ureters abnormal
Bladder abnormal
Unexplained oligohydramnios**
UTD A2-3: INCREASED RISK

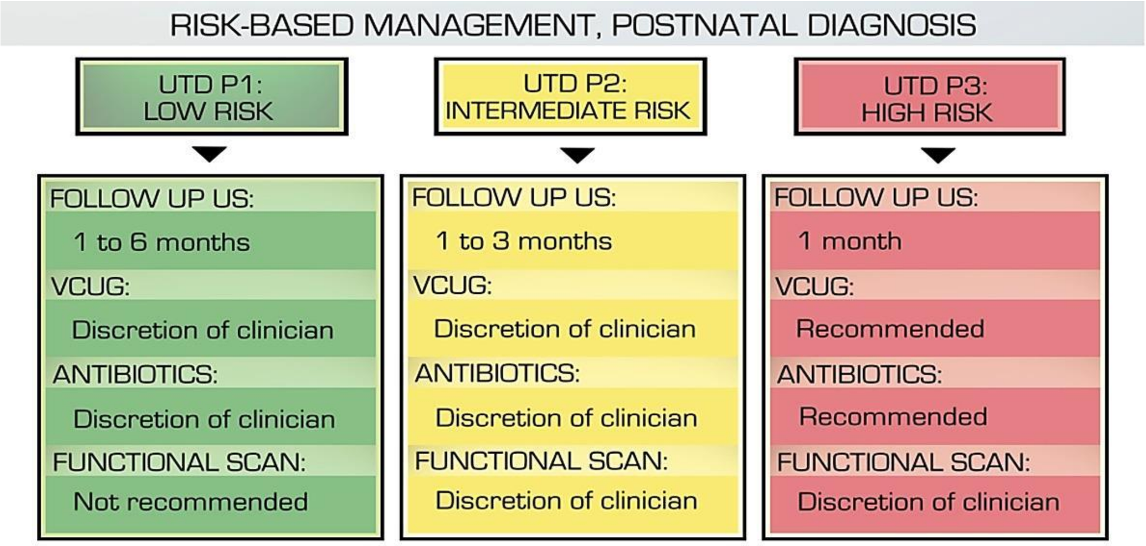
*Central and peripheral calyceal dilation may be difficult to evaluate early in gestation

**Oligohydramnios is suspected to result from a GU cause


RISK-BASED MANAGEMENT, PRENATAL DIAGNOSIS
UTD A1: LOW RISK
UTD A2-3: INCREASED RISK
PRENATAL PERIOD:
One additional US ≥ 32 weeks
AFTER BIRTH:
Two additional US:
1. > 48 hrs to 1 month
2. 1-6 months later
OTHER:
Aneuploidy risk modification if indicated
PRENATAL PERIOD:
Initially in 4 to 6 weeks*
AFTER BIRTH:
US at > 48 hours to 1 month of age*
OTHER:
Specialist consultation, e.g. nephrology, urology

*certain situations (e.g. posterior urethral valves, bilateral severe hydronephrosis) may require more expedient follow up

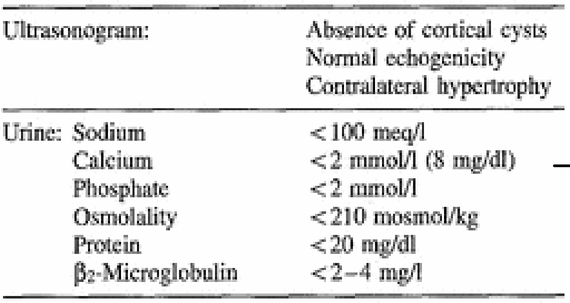

POSTNATAL PRESENTATION
> 48 hours APRPD 10 to < 15mm
> 48 hours APRPD ≥ 15mm
> 48 hours APRPD ≥ 15mm
Central calyceal dilation
Peripheral calyceal dilation
Peripheral calyceal dilation
Parenchymal thickness normal
Parenchymal thickness normal
Parenchymal thickness abnl
Parenchymal appearance normal
Parenchymal appearance normal
Parenchymal appearance abnl
Ureters normal
Ureters abnormal
Ureters abnormal
Bladder normal
Bladder normal
Bladder abnormal
UTD P1: LOW RISK
UTD P2: INTERMEDIATE RISK
UTD P3: HIGH RISK



The choice to utilize prophylactic antibiotics or recommend voiding cystourethrogram will depend on the suspected underlying pathology

- For **bilateral** cases, stratification of risk should be based on the grading of UT dilation in the **most severely affected side**.

- **Fetal intervention**: For fetuses with suspected lower urinary tract obstruction and oligohydramnios. Termination of pregnancy not recommended, except in presence of extrarenal life threatening abnormality
-
- Renal function and maturity may be predicted by **fetal vesicocentesis** done on **two/more** occasions.



Ultrasonogram:		Absence of cortical cysts Normal echogenicity Contralateral hypertrophy
Urine:	Sodium	< 100 meq/l
	Calcium	< 2 mmol/l (8 mg/dl)
	Phosphate	< 2 mmol/l
	Osmolality	< 210 mosmol/kg
	Protein	< 20 mg/dl
	β_2-Microglobulin	< 2–4 mg/l

→ Likely to **benefit** from intervention

- Intervention should be performed **only for severe oligohydramnios and "normal"-appearing kidneys**
- Intervention **may not change the long-term prognosis** of renal function or be a predictor for possible urinary diversion

9) Multicystic dysplastic kidney (MCDK)

I. Introduction

- MCDK is a **developmental anomaly resulting in multiple cysts of varying sizes, without identifiable normal renal parenchyma**. These kidneys have **no function** by definition, and usually the contralateral kidney is normal and exhibits compensatory hypertrophy. Only unilateral involvement is compatible with life.
- The kidney often **does not have a reniform** appearance, and it is typically associated with an **atretic ureter** with no connection between glomerulus and calyces.
- Typically, the kidney has the appearance of a **bunch of grapes, with little stroma between the cysts**.
- Renal size is highly variable, ranging from a small nubbin of tissue to a very large mass that fills most of the abdomen. In fact, MCDK is the **second most common cause of an abdominal mass in a newborn, after hydronephrosis.**

Incidence: 1 in 1000 to 1 in 4000 live births, Male preponderance (55-75%)

II. Types

MCDK can be of two types:

- **a)** The **infundibulopelvic type**, with the atresia involving both the renal pelvis and the ureter.
- **b)** The less common **hydronephrotic type**, in which only the upper ureter is atretic.

In both cases, the **ureters are absent or atretic and the renal vessels are hypoplastic**.
Associations: Secondary to ureterocele, one half of duplex (usually upper pole associated with ectopic ureter, horseshoe kidney

III. Etiology

Iit is a result of an error **in renal development**.
Theories:

- a) Obstruction theory – due to urinary obstruction during development
- b) Ureteric bud theory – ureteric bud and metanephric blastema interaction problem.

IV. Clinical features

Multicystic dysplasia is the **most common type of renal cystic disease and is the second most common cause of an abdominal mass in infants**.
The contralateral system frequently is abnormal.

- Contralateral UPJO – 3% to 12%
- Contralateral VUR 18% to 43%

The **natural history of MCDK is benign**; the incidence of complications is extremely rare; and approximately 40% of MCDKs will spontaneously involute.

No increased risk of hypertension or neoplasm (rare anecdotal reports of both)

V. Histopathology

Like any dysplastic kidneys **primitive duct** and embryonic elements are seen on histopathology

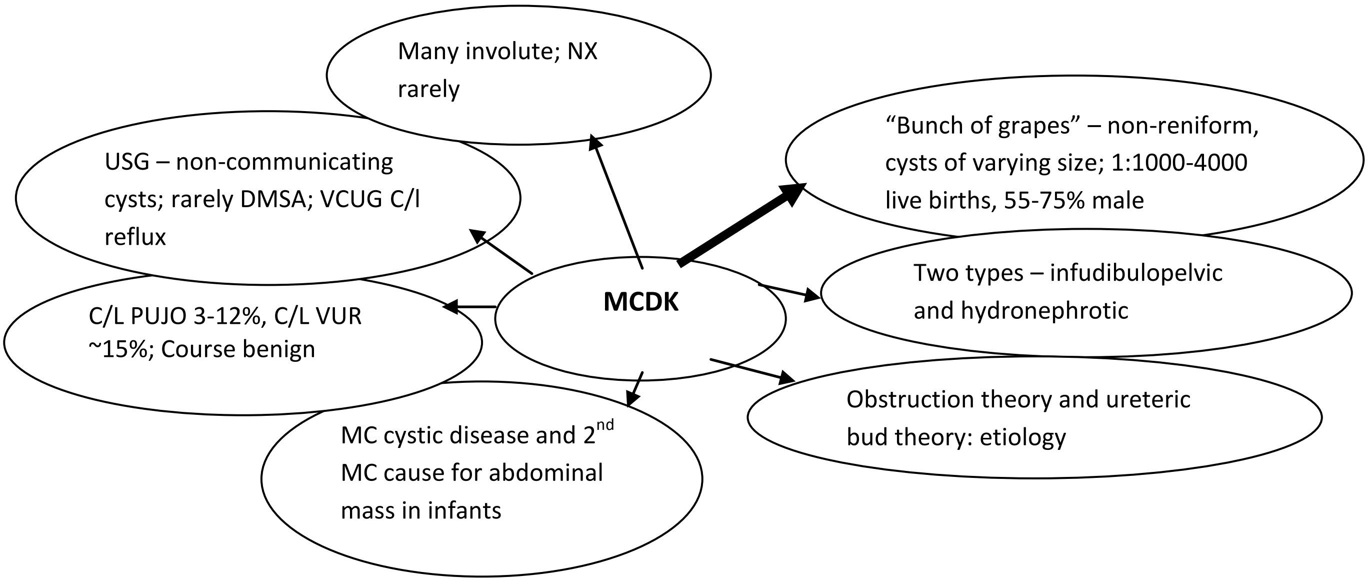
VI. Evaluation

- **Ultrasound** – non communicating cysts that are haphazard in distribution and of varying sizes without a large central or medial cyst
- **DMSA scan** may be rarely needed to differentiate from hydronephrosis
- **VCUG** – if suspecting contralateral functioning kidney reflux

VII. Treatment

- Rarely need active treatment – many involute and have benign course
- Surgery (nephrectomy) if very large mass with mass effect and rare cases associated with hypertension/carcinoma and to relieve pain secondary to cyst rupture/infection

Quick round-up


MCDK
Many involute; NX rarely
"Bunch of grapes" – non-reniform, cysts of varying size; 1:1000-4000 live births, 55-75% male
Two types – infudibulopelvic and hydronephrotic
Obstruction theory and ureteric bud theory: etiology
MC cystic disease and 2nd MC cause for abdominal mass in infants
C/L PUJO 3-12%, C/L VUR ~15%; Course benign
USG – non-communicating cysts; rarely DMSA; VCUG C/l reflux

10) Megaureter

Megaureter is the dilation of the ureter irrespective of the cause to **more than diameter of 7mm**.

Primary (intrinsic) or Secondary (neurogenic bladder, bladder outlet obstruction)
Types:

- Obstructive
- Refluxing
- Non obstructive, non-refluxing
- Refluxing and obstructing

Primary obstructive megaureter (**POM**) is due to adynamic segment in the distal ureter neat VUJ in the absence of other secondary causes.

Clinical features: Detected on antenatal ultrasound or may be symptomatic postnatally (pain, UTIs, stone formation, microscopic hematuria and renal dysfunction)

Evaluation:

Ultrasound, VCUG (to establish cause and rule out secondary causes) and functional imaging like DTPA renal scan.

Treatment:

- Aim of treatment is to preserve renal function.
- Asymptomatic patients with refluxing type megaureter with no associated complications may be managed conservatively.
- Surgery in the case of POM is to be considered when patients are **symptomatic** or have recurring UTIs, progressive unremitting dilatation on ultrasound, **differential renal function less than 40%, and/or significant decreases in differential renal function of 5% or greater on sequential “comparable” renal nuclear functional studies**.

Various options:

a) Urinary diversion – DJ stenting/PCN placement in setting of infection/severe pain
b) Endoscopic management – Balloon dilation of adynamic segment has been tried with lesser success rate
c) Ureteric reimplantation, with or without tapering. Reimplantation in a nonrefluxing fashion with adequate length-to-diameter ratio of **5: 1** so as to improve coaptation of the ureteral lumen whereby effective peristalsis and urine transportation are achieved. **Tapering/tailoring** can be achieved by **excision or plication** (placation usually used only for ureteric diameters upto **1.75cm**. Examples include Star placation and Kalcinski’s folding technique. Hendrens’ technique is an example for excisional tapering)
d) Nephrectomy – non functioning kidney

11) Developmental anomalies of the kidney and management options of their complications (very vague question – just a broad overview only)

Anomaly	**Complications**	**Management options**
Anomalies of number		
Bilateral renal agenesis	-40% still born; most others do not live beyond 48 hrs	Pulmonary hypoplasia is the cause
Unilateral renal agenesis	Other associated anomalies 50% probability of requiring dialysis in next 30 years	Management depending on system involved Periodic assessment for proteinuria and hypertension
Supernumary kidney	Rarely symptomatic Obstruction/infection/hypertension	

Anomalies of ascent Renal ectopia	Rarely ectopic ureter Stone/infection	Excision/reimplantation ESWL/PCNL/open or lap surgery
Anomalies of form and fusion Crossed ectopia Horse shoe kidney	Skeletal system involvement 60% asymptomatic One third PUJO Stone Cancer (1.76 – 7.93 times more incidence of Wilms tumor)	Orthopaedic consult Pyeloplasty/Diversion ESWL/PCNL/RIRS/open surgery Chemoptherapy/Surgery
Anomalies of rotation	Infection, obstruction, stone formation	Diversion/surgery
Anomalies of vasculature	Renal artery aneurysm Renal arteriovenous fistula	Interventional radiology/surgery Treatment depends on hemodynamic effect

12) Pediatric nephrolithiasis

- There has been an increase in the incidence of pediatric urolithiasis in recent years. The management of the urolithiasis differs with respect to etiology, metabolic causes, and evaluation and treatment options from adults.
- Improvement in instrumentation tailored for pediatric cases have increased the endourologic treatment options.

Clinical presentation:

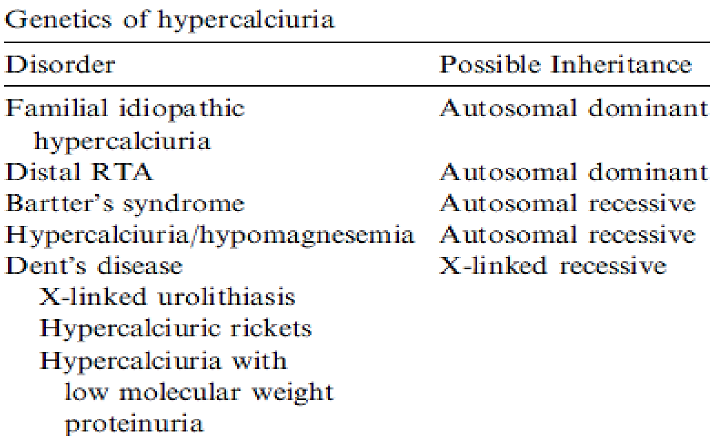
- The presentation in a child may be much more subtle depending on the age. The presentation can include pain, fever, LUTS depending on site and severity of obstruction the stone causes.
- In paediatric population, associated **metabolic** causes for stone formation can be present in as high as **50%** and few series describe associated anatomical **abnormalities in up to 30%.**
- Even in the paediatric population, calcium stones (oxalate and phosphate) constitute the bulk – 75% while infection stones account for 15-25%. Cystine stones constitute 2-10% of all paediatric stones.

Evaluation

The preliminary evaluation in paediatric stones should include metabolic work up in the form of 24 hour calcium, oxalate, uric acid and citrate in addition to urinalysis, urine culture, renal function test and serum PTH. Lab reference range for pediatric population varies and this has to be ensured. If collection of 24 hr sample is cumbersome in younger children spot samples with ratios can serve as a surrogate.

Also whenever possible the stone must be sent for stone analysis.

Stone disease in pediatric population has **genetic, anatomic, metabolic and dietary causes**. For example there are number of genetic causes for hypercalciuria alone that contribute to stone disease.



Genetics of hypercalciuria

Disorder	Possible Inheritance
Familial idiopathic hypercalciuria	Autosomal dominant
Distal RTA	Autosomal dominant
Bartter's syndrome	Autosomal recessive
Hypercalciuria/hypomagnesemia	Autosomal recessive
Dent's disease	X-linked recessive
X-linked urolithiasis	
Hypercalciuric rickets	
Hypercalciuria with low molecular weight proteinuria	

Imaging in paediatric urolithiasis

The goals of imaging remain the same – to determine stone location, size, density and urinary tract anatomy.

- NCCT has become the most accurate and efficient **first choice imaging with >95%** sensitivity and specificity irrespective of stone location. Limited sequences in the area of interest can decrease radiation exposure.
- USG has a more limited role – should be considered a screening tool in non emergent flank pain.
- IVU may be used if NCCT is not available. Further functional imaging in the form of DTPA/DMSA scan may be indicated in certain cases.

Treatment

a) Conservative managent

If there is no obstruction/infection, conservative management may be tried for renal calculi <3mm which are likely to spontaneously pass. Ureteric calculi >4mm are likely to require intervention.

b) ESWL

- Renal and proximal ureteric calculi upto 15mm may be managed with ESWL. The superior success rates of ESWL in children is attributed to **softer stone compostion, smaller relative stone volume, increased ureteral compliance to accommodate fragments and smaller body volume to facilitate shock transmission**.
- For younger children general anesthesia may be required.
- Pre-ESWL stenting may be considered in solitary kidneys, large stone bulk, obstruction or abnormal anatomy.
- The effects of shock on renal tissue in younger children are a concern. Also the need for multiple sessions for larger bulk stone makes this option less likely for larger stones. ESWL is also not effective against cystine stones and struvite stones.

c) Ureteroscopy/RIRS

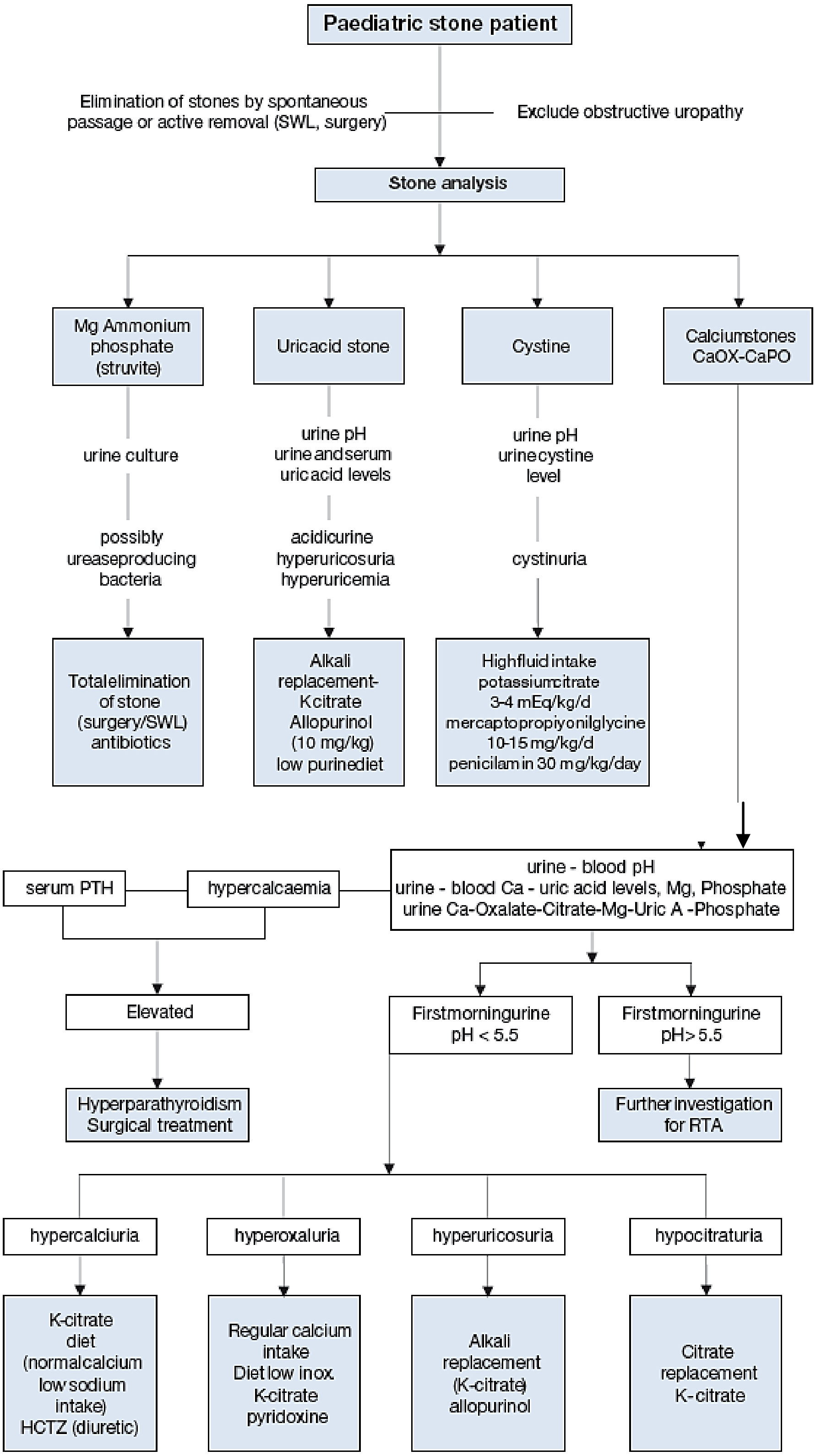
- With the availability of better **instrumentation** – smaller ureteroscopes, access sheaths, and flexible scopes – URS and RIRS for pediatric stones have increased.
- During both URS/RIRS and PCNL it should be ensured that isotonic solution and warmed fluids are used for irrigation to prevent **hyponatremia and hypothermia** for which this age population is more prone to.

d) PCNL

- PCNL is possible in children using adult equipments. However just like URS/RIRS there has been advancement in instrumentation for PCNL also and smaller size instruments are now available that decrease the blood loss and post operative pain.
- Many a times, **nephrocalcinosis** (hereditary tubulopathies, Vitamin D intoxication, medullary spong kindey) may mimick staghorn calculus and care has to exercised to avoid missing this entity as management is largely medical.
- PCNL is procedure of choice for **infection stones, cystine stones and staghorn calculi**.
- Shortest and most direct access should be attempted and for larger stones multiple punctures may be required

e) Medical management

- Every paediatric stone case should be managed **in consultation with a paediatric nephrologist** to ensure appropriate medical management such as alkalisation of the urine, thiazide addition (for cases of hypercalciuria), cystine chelators (such as penicillamine) and antibiotic prophylaxis for infection stones.
- These have to be dictated by the metabolic evaluation and etiology of the stone. In addition adequate hydration and periodic evaluation at follow up cannot be overemphasized.


Paediatric stone patient
Elimination of stones by spontaneous passage or active removal (SWL, surgery)
Exclude obstructive uropathy
Stone analysis
Mg Ammonium phosphate (struvite)
Uricacid stone
Cystine
Calciumstones CaOX-CaPO
urine culture
possibly ureaseproducing bacteria
Total elimination of stone (surgery/SWL) antibiotics
urine pH urine and serum uric acid levels
acidic urine hyperuricosuria hyperuricemia
Alkali replacement- K citrate Allopurinol (10 mg/kg) low purine diet
urine pH urine cystine level
cystinuria
High fluid intake potassium citrate 3-4 mEq/kg/d mercaptopropiyonilglycine 10-15 mg/kg/d penicilamin 30 mg/kg/day
urine - blood pH urine - blood Ca - uric acid levels, Mg, Phosphate urine Ca-Oxalate-Citrate-Mg-Uric A -Phosphate
serum PTH
hypercalcaemia
Elevated
Hyperparathyroidism Surgical treatment
First morning urine pH < 5.5
First morning urine pH > 5.5
Further investigation for RTA
hypercalciuria
hyperoxaluria
hyperuricosuria
hypocitraturia
K-citrate diet (normal calcium low sodium intake) HCTZ (diuretic)
Regular calcium intake Diet low in ox K-citrate pyridoxine
Alkali replacement (K-citrate) allopurinol
Citrate replacement K-citrate

13) Clean intermittent catheterisation (CIC)

- **Introduction**

  The major concern in the care of patients with urinary retention or incontinence due to acontractile or neuropathic bladder is **adequate bladder emptying, prevention of urinary tract infection and preservation of upper urinary tract function**.

- Clean intermittent catheterisation has been clearly established as the best way of achieving good bladder emptying and has transformed the lives of people rendered housebound by bladder problems. Once the initial apprehension is overcome, most people find intermittent catheterisation easy.

- Age and disability does not preclude a trial of intermittent catheterisation, and even patients with severe spinal deformity, absent perineal sensation, intention tremor, poor eyesight, etc., have been taught to catheterise themselves. Follow-up has shown that clean intermittent catheterisation gives good long-term results.

History

Guttman and Frankel (1967) pioneered the use of intermittent catheterisation in spinal units. They advocated the use of **sterile** catheters and strict asepsis and stressed that the procedure should be performed by medical personnel, in order to prevent infection.

A different view of the origin of urinary infection in intermittently catheterised patients was expressed by **Lapides** (1972). He proposed that a **decreased blood flow to the renal tissue, ureter, bladder, and urethra due to over distension of the bladder and high intravesical pressure was the most frequent mechanism of the genesis of infection**. It was postulated that the tissues became vulnerable to infection by invading gram negative organisms from the patient's own gut via **haematogenous and lymphogenous routes** and that the bacterial flora of the urethra and vagina were of little importance. Any bacteria introduced into the bladder by the catheter would be neutralised by the resistance of the host, **provided that an adequate blood supply was maintained to the tissues**. On the basis of this hypothesis, Lapides devised a nonsterile "Clean" intermittent-self-catheterisation technique and proved it to be safe and effective. Intermittent catheterisation was thus made simple and could be incorporated into a daily routine.

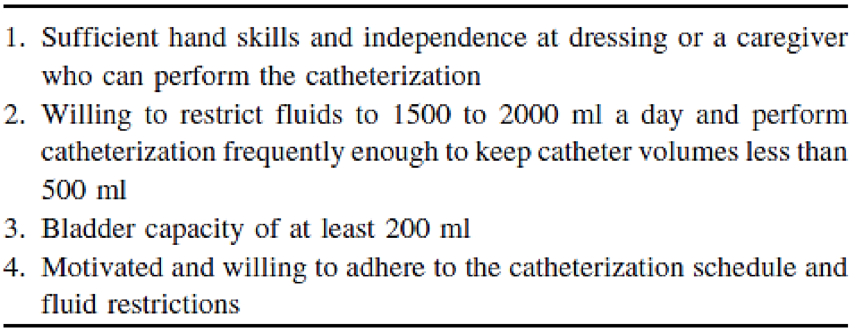
Effects of Intermittent Catheterisation

a) Bladder empties completely and ender the patient's control (Continence): By eliminating residual urine, intermittent catheterisation enables the bladder to function more effectively as a reservoir.
b) Reduces symptomatic urinary infection: As residual urine is eliminated, urinary stasis leading to urinary infection and calculi is reduced.
c) Prevention or Improvement of upper urinary tract dilatation: Sphincter overactivity leading to outlet obstruction, detrusor sphincter dyssynergia, and high intravesical pressures is responsible for upper tract dilation by impeding drainage of urine from the kidneys and/or causing vesicoureteric reflux. Infection increases the risk of upper tract damage. Intermittent catheterisation preserves the upper tract by eliminating residual urine, decreasing intravesical pressure and reducing urinary infection.

Prerequisites

a) Adequate bladder capacity: Large residual urine is a good indicator of bladder capacity. The greater the volume of residual urine, the better is the prospects of the patient remaining dry in between catheterisations. Patients with hyper-reflexia require anticholinergic drugs to attain a storing capacity and if still not achieved, they may require augmentation.
b) Sphincter activity: Adequate sphincter activity is also indicated by the presence of residual urine. Drugs and/or surgery may be required in some to achieve this.
c) Motivation: Motivation is absolutely essential for the success of this program.

Patients most likely to be successful on CIC are as follows:



1. Sufficient hand skills and independence at dressing or a caregiver who can perform the catheterization
2. Willing to restrict fluids to 1500 to 2000 ml a day and perform catheterization frequently enough to keep catheter volumes less than 500 ml
3. Bladder capacity of at least 200 ml
4. Motivated and willing to adhere to the catheterization schedule and fluid restrictions

Indications

- Neuropathic bladder (Spinal dysraphism, Multiple Sclerosis, Spinal cord tumour and Injury, Disc prolapse, Diabetic neuropathy, Transverse Myelitis, Unknown).
- Acontractile bladder.
- Post operative retention.
- Following bladder reconstruction (Augmentation Cystoplasty, Continent Reservoir).

Procedure

Assessment

Physical examination should include assessment of spinal deformities, hand movements, eyesight, and sensation in the saddle area. Relevant investigations should be carried out to establish a diagnosis, as well as to serve as a baseline for future comparison.

Teaching Catheterisation

Intermittent catheterisation is best taught with the patient admitted to the hospital as this gives an opportunity to closely observe the patient during the learning process. It may also be wise to cover the initial few days with antibiotics till the technique is perfected. A doctor, continence adviser or a specially trained nurse takes charge of the education, and must explain the rationale and benefits, reassuring the patient that intermittent catheterisation is not painful, difficult or dangerous. Clear **diagrams** help the patient in understanding the anatomy. The **support of a fellow user** of intermittent catheterisation is invaluable. A booklet or a list of "do's and don'ts" can be a very useful aid.

The lesson starts with emphasis on **thorough cleaning of the hands and perineal area / penis with soap and water**. The catheter is then washed with water. After washing the hands and catheter, the patient must be instructed not to touch any contaminated area. The female subject sits on the examination table with feet on the table, lower limbs flexed and knees held apart. In the sitting position the patient is able to visualise the perineum in a mirror at the foot of the table. The labia are separated and the subject is instructed to insert the catheter through the urethral meatus into the bladder holding the catheter 2 cm from the tip. With practice the patient learns to locate the meatus without the mirror by just feeling for the meatus. Male patients may learn the technique in the sitting or standing position and are advised to use a water-soluble lubricant for easy catheterisation. Once urine starts to flow out the patient is instructed to pass the catheter in for 2 cm more. Once urine has stopped flowing the catheter should be rotated and suprapubic pressure given. Then the catheter is withdrawn slowly. If urine starts to drain during withdrawal, the patient is instructed to wait with the catheter at that level till the urine stops flowing. These simple measures ensure that the bladder is completely emptied. The patient is warned never to forego catheterisation even when soap and water are not available but to catheterise at the prescribed time with the best available measures.

How often to catheterise

Catheterisation must be frequent enough to prevent the bladder becoming overdistended and to keep the patient dry. Patients should normally catheterise at least four times a day, more frequently in children, in patients with a high fluid intake, and in patients with a small capacity bladder. The volume obtained on catheterisation gives an estimate of bladder capacity and suggests how much can be drunk between catheterisation if the patient is to remain dry. This volume should ideally be kept around **300 ml**. Patients soon learn to balance fluid intake with frequency of catheterisation in order to remain dry. To ensure timely catheterisation the technique is kept simple. No bedtime drink is to be taken, unless the patient catheterises during the night. A daily intake of 2 L is sufficient.

Catheters and Catheter Care

Foleys catheter or Nelatons catheter may be used. Keeping the catheter clean and dry is all that is required, and has been **compared to the care of the toothbrush**. After use, the outer surface of the catheter may be washed with soap and water and the inside with clean water. Water inside the catheter is then thoroughly wrung out and the catheter carried in a dry state in a clean container. The catheter may be re-used, and there is no fixed period of time for usage. A common sense approach is applied and the catheter is changed when it gets dirty or damaged.

Role of antiseptics and antibiotics: **No role in routinely.**

Antibiotics seem to have a very limited role. All clinical infections are treated with antibiotics. Bacteriuria need not be treated except in patients with severe upper tract damage/high grade reflux and in the immunocompromised (Renal Transplant). Antibiotic prophylaxis is also recommended in this group. Therapeutic antibiotics are to be used in infections with stone-forming organisms (e.g. Proteus) even if asymptomatic.

Follow-Up

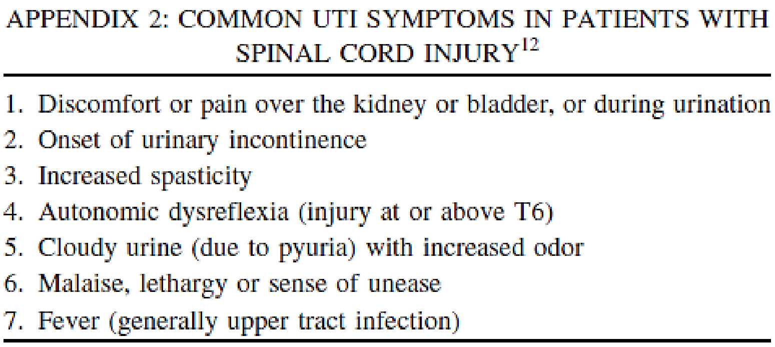
Patients should be seen frequently till they are confident about the technique. **Ultrasound** residual urine measurement may be done to ensure that the bladder is being completely emptied. In the male sphincter spasm may prevent the catheter from entering the bladder. Waiting at this level with gentle pressure or the use of a stiffer, narrower, curved catheter may be effective. Long-term follow-up with blood biochemistry/urine culture and upper-tract imaging is also essential.

Results

Favourable results have been obtained with UTI rates, acceptance of proceudure, continence and upper tract status

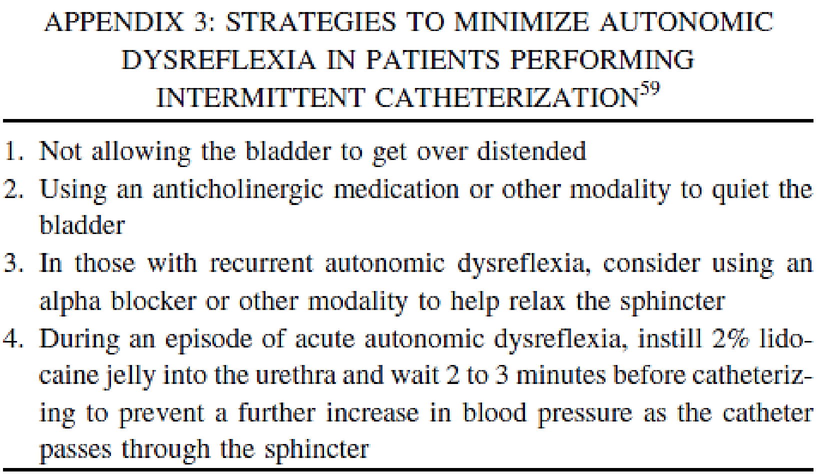
Complications

- UTIs
- Bladder stone
- Urethral trauma/stricture
- Autonomic dyreflexia



APPENDIX 2: COMMON UTI SYMPTOMS IN PATIENTS WITH SPINAL CORD INJURY[12]

1. Discomfort or pain over the kidney or bladder, or during urination
2. Onset of urinary incontinence
3. Increased spasticity
4. Autonomic dysreflexia (injury at or above T6)
5. Cloudy urine (due to pyuria) with increased odor
6. Malaise, lethargy or sense of unease
7. Fever (generally upper tract infection)



APPENDIX 3: STRATEGIES TO MINIMIZE AUTONOMIC DYSREFLEXIA IN PATIENTS PERFORMING INTERMITTENT CATHETERIZATION[59]

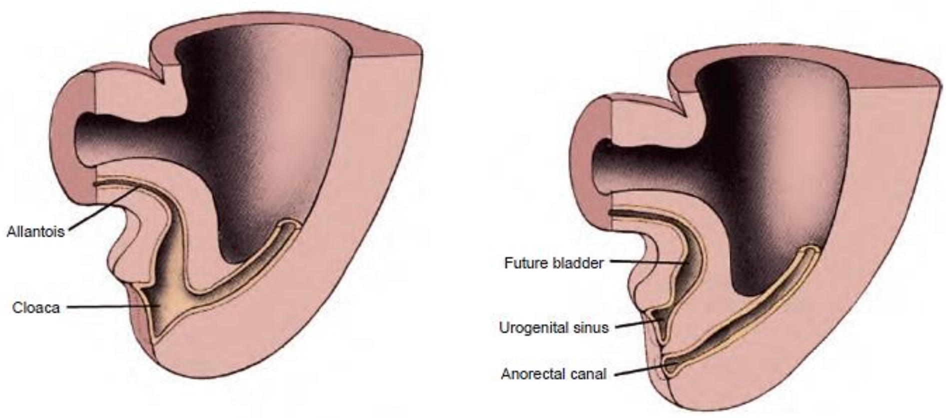
1. Not allowing the bladder to get over distended
2. Using an anticholinergic medication or other modality to quiet the bladder
3. In those with recurrent autonomic dysreflexia, consider using an alpha blocker or other modality to help relax the sphincter
4. During an episode of acute autonomic dysreflexia, instill 2% lidocaine jelly into the urethra and wait 2 to 3 minutes before catheterizing to prevent a further increase in blood pressure as the catheter passes through the sphincter

14) Development of trigone and bladder

Formation of Urogenital Sinus

- At the **third week** of gestation the cloacal membrane remains a bilaminar structure composed of endoderm and ectoderm.
- During the fourth week the neural tube and the tail of the embryo grow dorsally and caudally, projecting over the cloacal membrane and this differential growth of the body results in embryo folding.
- The cloacal membrane is now turned to the ventral aspect of the embryo, and the terminal portion of the endoderm-lined yolk sac dilates and becomes the ***cloaca.***
- According to the theories of Rathke and Tourneux regarding embryonic development, the **partition of the cloaca** into an **anterior urogenital sinus and a posterior anorectal canal** occurs by the midline fusion of two lateral ridges of the cloacal wall and by a descending urorectal septum. This process is thought to occur during the **fifth and sixth weeks**, and it culminates with the fusion of this urorectal septum with the cloacal membrane.

- However, some investigators have challenged this classic view with evidence that there is neither a descending septum nor fusing lateral ridges of the cloacal wall. There is further evidence that the urorectal septum never fuses with the cloacal membrane.
- According to these observations the congenital cloacal and anorectal malformations, which were previously thought to occur because of a failure of septum formation and its fusion with the cloacal membrane, may in fact occur from an abnormal development of the cloacal membrane itself.
- The nephric (wolffian) duct fuses with the cloaca by the 24th day and remains with the urogenital sinus during the cloacal separation.
- **The entrance of the nephric duct into the primitive urogenital sinus serves as a landmark distinguishing the cephalad vesicourethral canal from the caudal urogenital sinus**.
- **The vesicourethral canal gives rise to the bladder and pelvic urethra, whereas the caudal urogenital sinus forms the phallic urethra for males and distal vaginal vestibule for females**.



Development of the urogenital sinus. Between the fourth and sixth weeks the cloaca is divided into an anterior urogenital sinus and a posterior anorectal canal. The superior part of the urogenital sinus, continuous with the allantois, forms the bladder. The constricted narrowing at the base of the urogenital sinus forms the pelvic urethra. The distal expansion of the urogenital sinus forms the vestibule of the vagina in females and the penile urethra in males.

Formation of Trigone

- By day 33 of gestation, the *common excretory ducts* (the portion of nephric ducts distal to the origin of ureteric buds) dilate and connect to the urogenital sinus.
- The formation of these final connections involves apoptosis, which enables the ureters to disconnect from the nephric ducts, and fusion, in which the ureteral orifice inserts into the urogenital sinus epithelium at the level of the trigone
- According to the **classic view**, the **right and left common excretory ducts fuse in the midline as a triangular area**, forming the primitive trigone, structurally different from bladder and urethra.
- The ureteral orifice exstrophies and evaginates into the bladder by day 37 and begins to migrate in a cranial and lateral direction within the floor of the bladder.
- During this process the nephric duct orifice diverges away from the ureteral orifice and migrates caudally, flanking the paramesonephric (müllerian) duct at the level of the urogenital sinus. This is the site of the future verumontanum in males and vaginal canal in females.

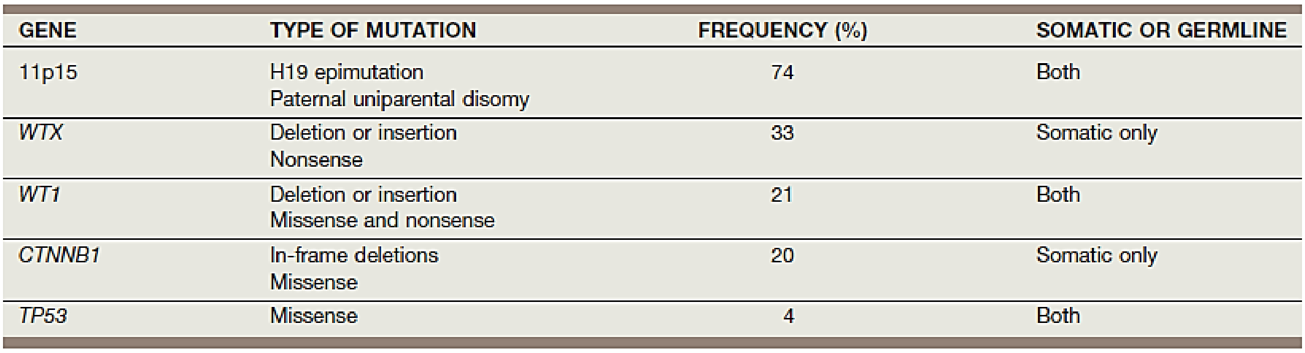
- Studies, however, have challenged this classic mechanism of trigone development. With use of the cell lineage studies in mice, the trigone was found to form mostly from bladder smooth muscle cells with only a minor contribution from the ureter.
- **To summarize the trigone is mesodermal in origin according to classic view (from fused common nephric ducts) whereas current opinion is that it is also endodermal like rest of the bladder**.

15) Genetics, pathology and management of Wilms' tumor

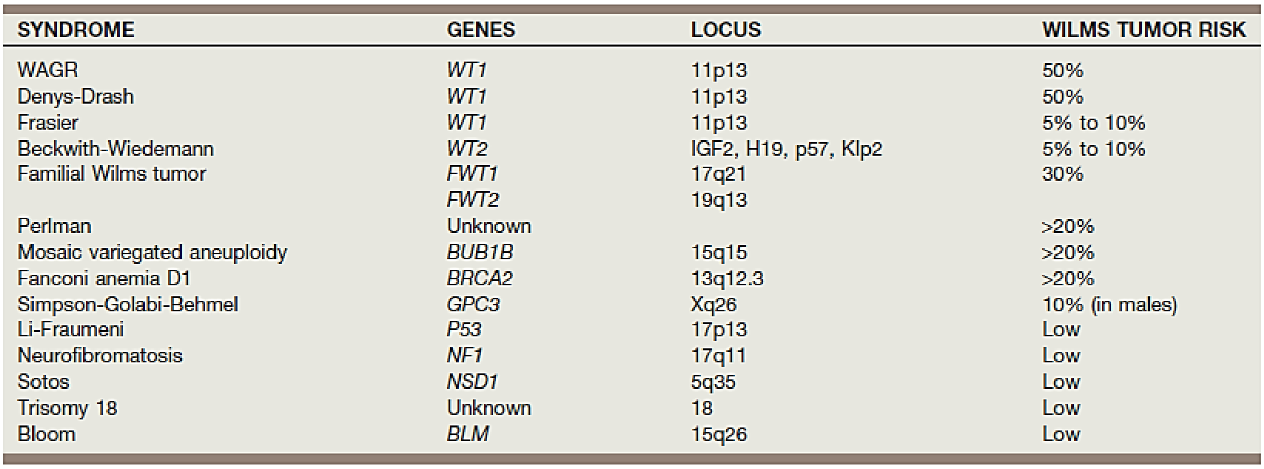
- Wilms tumor/nephroblastoma is the **most common primary malignant renal tumor of childhood (accounts for 6-7% of all childhood cancers)**.
- It develops from embryonic remnants (**nephrogenic rests**) of the kidney.
- With current day management strategies, Wilms tumor has excellent outcomes with 5 year overall survival reaching 90%.
- Median age at presentation is **3.5 years** with slight male predominance (in North America slight female predominace found).
- **1-2% of tumors are familial, 5-10% bilateral and 10% are associated with congenital anomalies/syndromes**.

I. Genetics

Wilms tumor has been associated with loss of function mutations of a number of tumor suppressor and transcription genes. These include mutations of the WT1, p53, FWT1, and FWT2 genes, and at the 11p15.5 locus. Wilms tumor **does not** follow Knoudsons two hit hypothesis.



GENE	TYPE OF MUTATION	FREQUENCY (%)	SOMATIC OR GERMLINE
11p15	H19 epimutation Paternal uniparental disomy	74	Both
WTX	Deletion or insertion Nonsense	33	Somatic only
WT1	Deletion or insertion Missense and nonsense	21	Both
CTNNB1	In-frame deletions Missense	20	Somatic only
TP53	Missense	4	Both



Syndromes Associated with Development of Wilms Tumor

SYNDROME	GENES	LOCUS	WILMS TUMOR RISK
WAGR	*WT1*	11p13	50%
Denys-Drash	*WT1*	11p13	50%
Frasier	*WT1*	11p13	5% to 10%
Beckwith-Wiedemann	*WT2*	IGF2, H19, p57, Klp2	5% to 10%
Familial Wilms tumor	*FWT1*	17q21	30%
	FWT2	19q13	
Perlman	Unknown		>20%
Mosaic variegated aneuploidy	*BUB1B*	15q15	>20%
Fanconi anemia D1	*BRCA2*	13q12.3	>20%
Simpson-Golabi-Behmel	*GPC3*	Xq26	10% (in males)
Li-Fraumeni	*P53*	17p13	Low
Neurofibromatosis	*NF1*	17q11	Low
Sotos	*NSD1*	5q35	Low
Trisomy 18	Unknown	18	Low
Bloom	*BLM*	15q26	Low

Syndrome	Clinical features	Risk of Wilms
WAGR	Wilms, Aniridia, Genitourinaty anomalies and mental Retardation	50%
Denys-Drash	Male pseudohermaphroditism, renal mesangial sclerosis and Wilms	50%
Beckwith Weidmann	Macroglossia, hemihypertrophy, nephromegaly, hepatomegaly	5-10%

Other chromosomal abnormalities

Loss of heterozygosity **(LOH) of 1p and 16q** are associated with increased risk of tumor relapse and death. There are incorporated as prognostic molecular markers in the management.

II. Pathology

On gross, Wilms has a pseudocapsule with areas of hemorrhage and necrosis.
On HPE, Classical Wilms tumor has:

- Compact undifferentiated **blastema**
- Variable **epithelial** differentiation (embryonic tubules, rosettes and glomeruloid structures)
- Significant **stromal** component separating the above

Wilms with predominantly epithelial differentiation have low aggressiveness and majority are Stage I tumors, however if they present as advanced stage they are more resistant to chemotherapy.

Anaplasia: **Anaplasia** confers poor histopathological prognosis even if tumor is confined to kidney and anaplastic tumors are resistant to chemotherapy.

Nephogenic rests:

- Perilobar nephrogenic rests (**PLNR**) are expressed later in embryogenesis and these are associated with contralateral synchronous tumor and hence need surveillance
- Intralobar nephrogenic rests (**ILNR**) are expressed earlier in embryogenesis and have stromal rich histology

Nephroblastomatosis – multiple nephrogenic rests with diffuse overgrowth of PLNRs may produce a thick rind that enlarges the kidney but preserves original shape. Increased anaplasia has been associated post chemotherapy in nephroblastomatosis.

III. Clinical presentation

- Most children with Wilms tumor present with an abdominal mass or swelling, without other signs or symptoms.

- Other symptoms can include abdominal pain (30 to 40 percent of patients), hematuria (12 to 25 percent), fever, and hypertension (25 percent).

- A subset of patients with subcapsular hemorrhage can present with rapid abdominal enlargement, anemia, hypertension, and sometimes fever.

- Although the lung is the most common metastatic site, children rarely present with respiratory symptoms.

- Physical examination reveals a firm, **nontender**, smooth mass that is eccentrically located and rarely crosses the midline.

- Once a Wilms tumor is suspected, subsequent abdominal examinations should be performed carefully. Vigorous palpation may rupture the renal capsule, resulting in tumor spillage, which increases the tumor stage and the need for more intensive therapy.

IV. Management

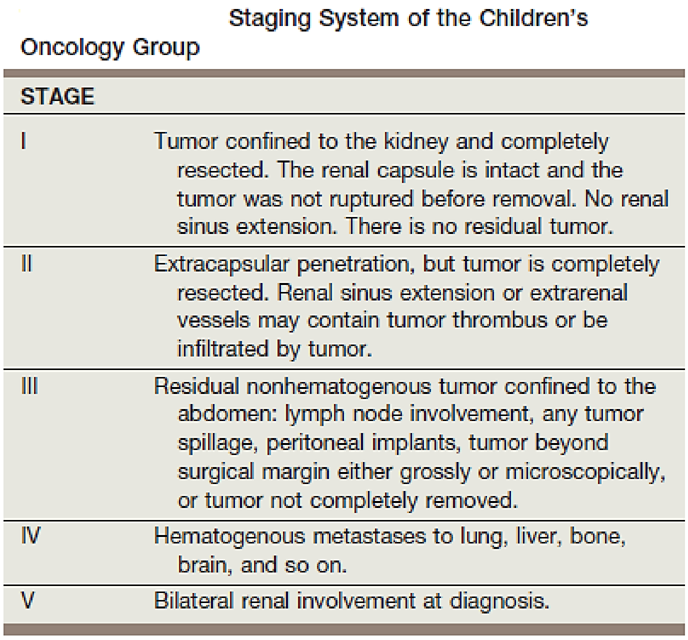
- Imaging includes ultrasound, CT/MRI and chest XRAY (chest CT may also be obtained if suspecting lung metastasis – lung is the most common site for metastasis)

- The two study groups for Wilms tumor are National Wilms Tumor Study (**NWTS**) which has now been unified into Childrens Oncology Group (**COG**) and **SIOP** (International Society of Paediatric Oncology)

- NWTS/COG is practised throughout North America and Canada while SIOP is used in Europe (also in Australia and some parts of South America).

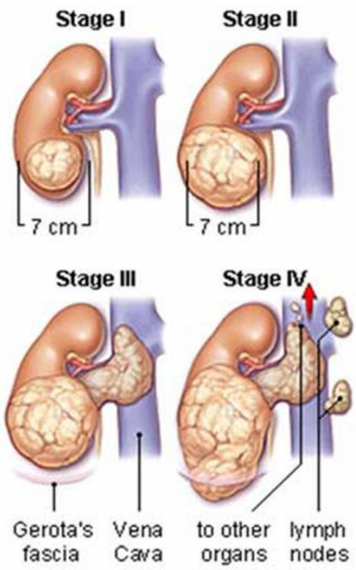
- The **fundamental difference is that in NWTS/COG guidelines chemotherapy is given after surgery while SIOG recommends pre-op chemothrerapy followed by surgery**. Hence even in the staging of the tumor in NWTS the staging is based on surgical evaluation prior to chemotherapy while SIOG staging evaluation is based on surgery after chemotherapy.

Staging



Staging System of the Children's Oncology Group

STAGE	
I	Tumor confined to the kidney and completely resected. The renal capsule is intact and the tumor was not ruptured before removal. No renal sinus extension. There is no residual tumor.
II	Extracapsular penetration, but tumor is completely resected. Renal sinus extension or extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed.
IV	Hematogenous metastases to lung, liver, bone, brain, and so on.
V	Bilateral renal involvement at diagnosis.

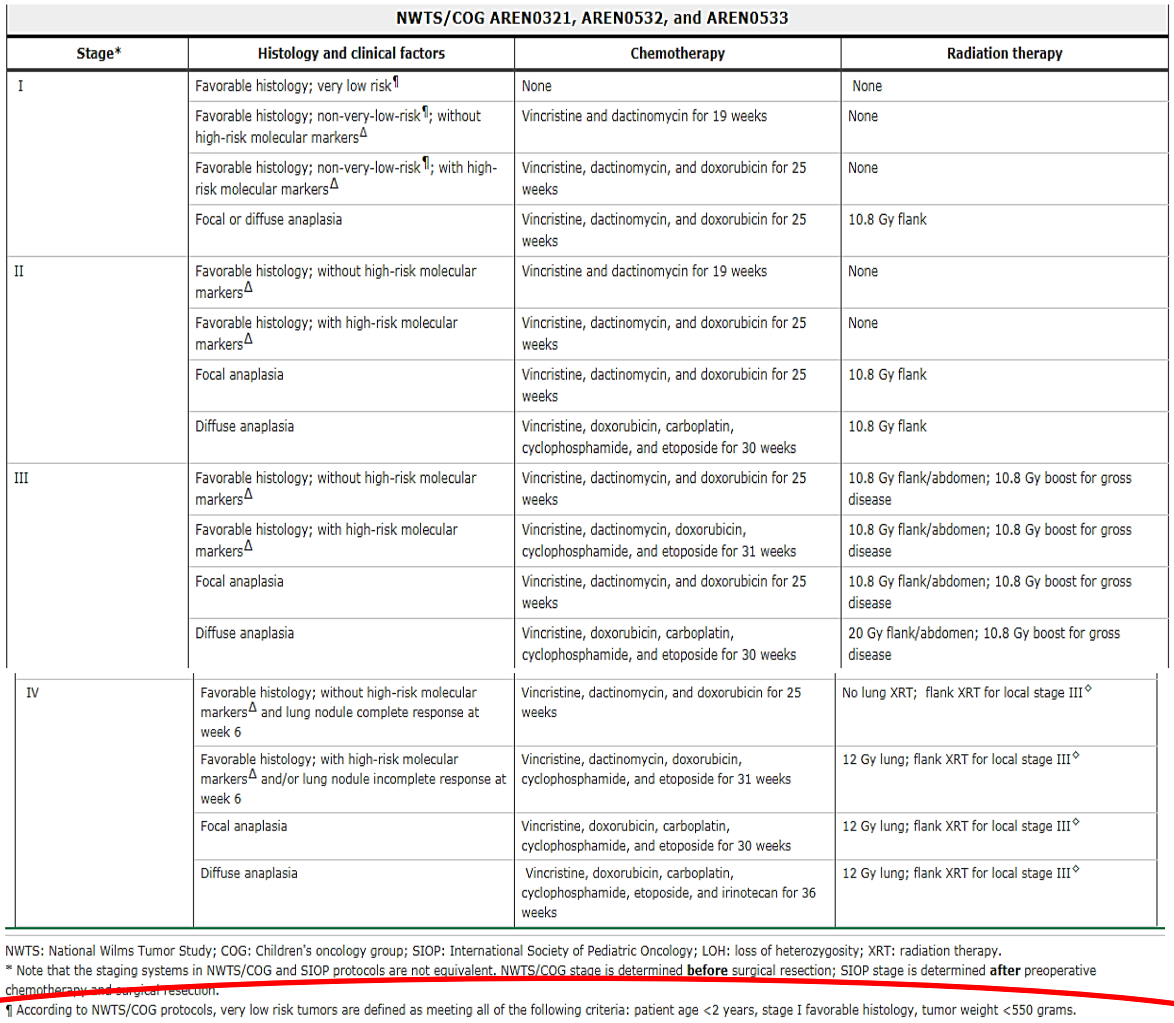


Advantages of each of the schools of thought

NWTS/COG	SIOP
Accurate assessment of HPE and extent	Decreases tumor volume, hence surgery becomes easier and lesser chance of tumor rupture/spillage (this would avoid RT)
Avoids chemotherapy in a small percentage of patients that turn out to be benign	Marker of in-vivo tumor sensitivity and more conservative approach for those that responded very well
Avoids delay in treatment	An UK study showed there was favourable down staging of tumors
	Lesser surgical complications

However both approaches and protocols have excellent outcomes and comparable 5 year overall survival rates in the range of 90%.

The following tables summarize the management protocol of the two groups based on staging and prognostic factors.



NWTS/COG AREN0321, AREN0532, and AREN0533

Stage*	Histology and clinical factors	Chemotherapy	Radiation therapy
I	Favorable histology; very low risk[¶]	None	None
	Favorable histology; non-very-low-risk[¶]; without high-risk molecular markers[Δ]	Vincristine and dactinomycin for 19 weeks	None
	Favorable histology; non-very-low-risk[¶]; with high-risk molecular markers[Δ]	Vincristine, dactinomycin, and doxorubicin for 25 weeks	None
	Focal or diffuse anaplasia	Vincristine, dactinomycin, and doxorubicin for 25 weeks	10.8 Gy flank
II	Favorable histology; without high-risk molecular markers[Δ]	Vincristine and dactinomycin for 19 weeks	None
	Favorable histology; with high-risk molecular markers[Δ]	Vincristine, dactinomycin, and doxorubicin for 25 weeks	None
	Focal anaplasia	Vincristine, dactinomycin, and doxorubicin for 25 weeks	10.8 Gy flank
	Diffuse anaplasia	Vincristine, doxorubicin, carboplatin, cyclophosphamide, and etoposide for 30 weeks	10.8 Gy flank
III	Favorable histology; without high-risk molecular markers[Δ]	Vincristine, dactinomycin, and doxorubicin for 25 weeks	10.8 Gy flank/abdomen; 10.8 Gy boost for gross disease
	Favorable histology; with high-risk molecular markers[Δ]	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide for 31 weeks	10.8 Gy flank/abdomen; 10.8 Gy boost for gross disease
	Focal anaplasia	Vincristine, dactinomycin, and doxorubicin for 25 weeks	10.8 Gy flank/abdomen; 10.8 Gy boost for gross disease
	Diffuse anaplasia	Vincristine, doxorubicin, carboplatin, cyclophosphamide, and etoposide for 30 weeks	20 Gy flank/abdomen; 10.8 Gy boost for gross disease
IV	Favorable histology; without high-risk molecular markers[Δ] and lung nodule complete response at week 6	Vincristine, dactinomycin, and doxorubicin for 25 weeks	No lung XRT; flank XRT for local stage III[◇]
	Favorable histology; with high-risk molecular markers[Δ] and/or lung nodule incomplete response at week 6	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide for 31 weeks	12 Gy lung; flank XRT for local stage III[◇]
	Focal anaplasia	Vincristine, doxorubicin, carboplatin, cyclophosphamide, and etoposide for 30 weeks	12 Gy lung; flank XRT for local stage III[◇]
	Diffuse anaplasia	Vincristine, doxorubicin, carboplatin, cyclophosphamide, etoposide, and irinotecan for 36 weeks	12 Gy lung; flank XRT for local stage III[◇]

NWTS: National Wilms Tumor Study; COG: Children's oncology group; SIOP: International Society of Pediatric Oncology; LOH: loss of heterozygosity; XRT: radiation therapy.

* Note that the staging systems in NWTS/COG and SIOP protocols are not equivalent. NWTS/COG stage is determined **before** surgical resection; SIOP stage is determined **after** preoperative chemotherapy and surgical resection.

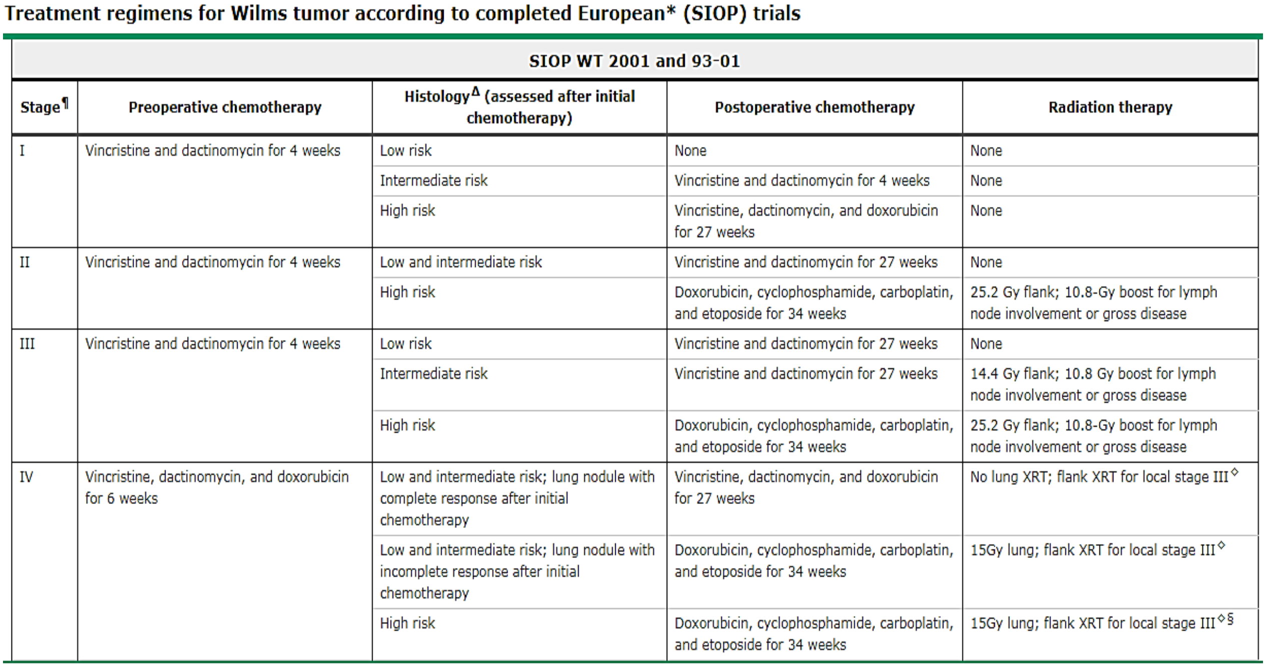
[¶] According to NWTS/COG protocols, very low risk tumors are defined as meeting all of the following criteria: patient age <2 years, stage I favorable histology, tumor weight <550 grams.

[Δ] According to NWTS/COG protocols, high-risk molecular markers refers to combined loss of heterozygosity [LOH] at chromosomes 1p and 16q.

[◇] Metastatic sites other than lung were also irradiated; XRT dose varied according to metastatic site.

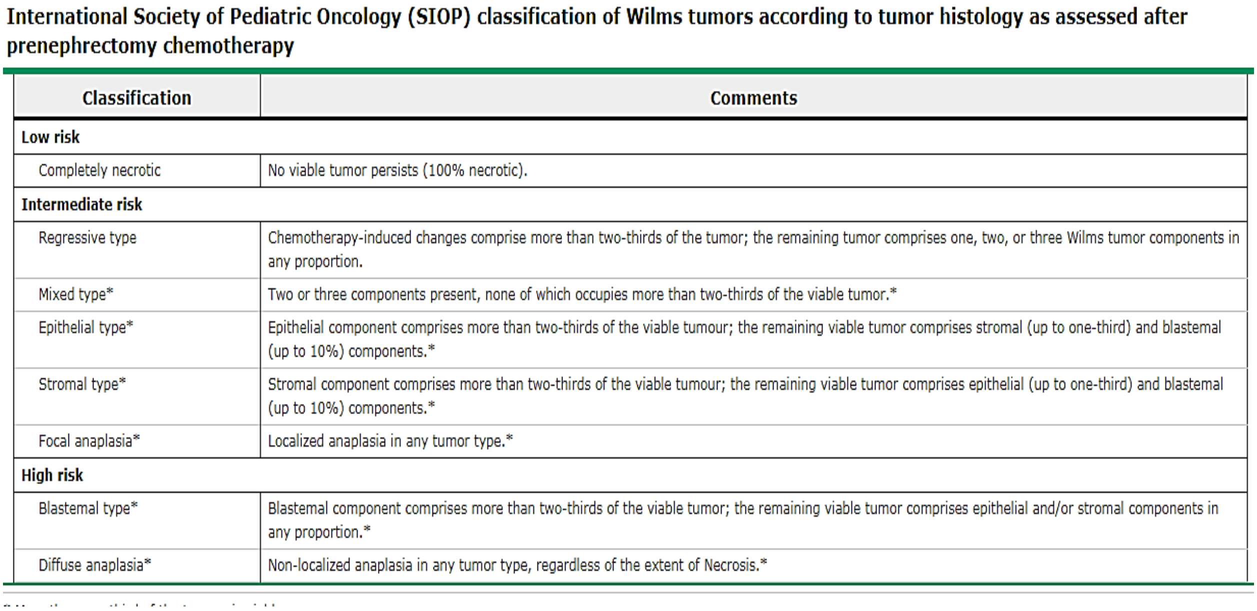
Favourable histology according to NWTS/COG is the absence of anaplasia

Very low risk tumors are ALL of <2yrs age, Stage I FH, weight <550g



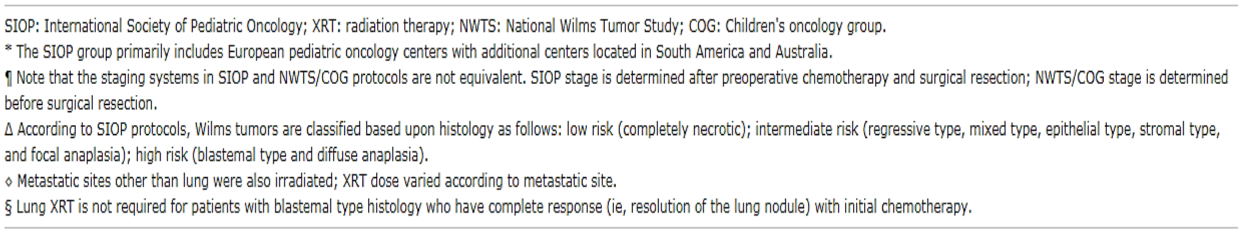
Treatment regimens for Wilms tumor according to completed European* (SIOP) trials

SIOP WT 2001 and 93-01				
Stage[¶]	**Preoperative chemotherapy**	**Histology[Δ] (assessed after initial chemotherapy)**	**Postoperative chemotherapy**	**Radiation therapy**
I	Vincristine and dactinomycin for 4 weeks	Low risk	None	None
		Intermediate risk	Vincristine and dactinomycin for 4 weeks	None
		High risk	Vincristine, dactinomycin, and doxorubicin for 27 weeks	None
II	Vincristine and dactinomycin for 4 weeks	Low and intermediate risk	Vincristine and dactinomycin for 27 weeks	None
		High risk	Doxorubicin, cyclophosphamide, carboplatin, and etoposide for 34 weeks	25.2 Gy flank; 10.8-Gy boost for lymph node involvement or gross disease
III	Vincristine and dactinomycin for 4 weeks	Low risk	Vincristine and dactinomycin for 27 weeks	None
		Intermediate risk	Vincristine and dactinomycin for 27 weeks	14.4 Gy flank; 10.8 Gy boost for lymph node involvement or gross disease
		High risk	Doxorubicin, cyclophosphamide, carboplatin, and etoposide for 34 weeks	25.2 Gy flank; 10.8-Gy boost for lymph node involvement or gross disease
IV	Vincristine, dactinomycin, and doxorubicin for 6 weeks	Low and intermediate risk; lung nodule with complete response after initial chemotherapy	Vincristine, dactinomycin, and doxorubicin for 27 weeks	No lung XRT; flank XRT for local stage III[◊]
		Low and intermediate risk; lung nodule with incomplete response after initial chemotherapy	Doxorubicin, cyclophosphamide, carboplatin, and etoposide for 34 weeks	15Gy lung; flank XRT for local stage III[◊]
		High risk	Doxorubicin, cyclophosphamide, carboplatin, and etoposide for 34 weeks	15Gy lung; flank XRT for local stage III[◊§]



International Society of Pediatric Oncology (SIOP) classification of Wilms tumors according to tumor histology as assessed after prenephrectomy chemotherapy

Classification	Comments
Low risk	
Completely necrotic	No viable tumor persists (100% necrotic).
Intermediate risk	
Regressive type	Chemotherapy-induced changes comprise more than two-thirds of the tumor; the remaining tumor comprises one, two, or three Wilms tumor components in any proportion.
Mixed type*	Two or three components present, none of which occupies more than two-thirds of the viable tumor.*
Epithelial type*	Epithelial component comprises more than two-thirds of the viable tumour; the remaining viable tumor comprises stromal (up to one-third) and blastemal (up to 10%) components.*
Stromal type*	Stromal component comprises more than two-thirds of the viable tumour; the remaining viable tumor comprises epithelial (up to one-third) and blastemal (up to 10%) components.*
Focal anaplasia*	Localized anaplasia in any tumor type.*
High risk	
Blastemal type*	Blastemal component comprises more than two-thirds of the viable tumor; the remaining viable tumor comprises epithelial and/or stromal components in any proportion.*
Diffuse anaplasia*	Non-localized anaplasia in any tumor type, regardless of the extent of Necrosis.*



SIOP: International Society of Pediatric Oncology; XRT: radiation therapy; NWTS: National Wilms Tumor Study; COG: Children's oncology group.

* The SIOP group primarily includes European pediatric oncology centers with additional centers located in South America and Australia.

¶ Note that the staging systems in SIOP and NWTS/COG protocols are not equivalent. SIOP stage is determined after preoperative chemotherapy and surgical resection; NWTS/COG stage is determined before surgical resection.

Δ According to SIOP protocols, Wilms tumors are classified based upon histology as follows: low risk (completely necrotic); intermediate risk (regressive type, mixed type, epithelial type, stromal type, and focal anaplasia); high risk (blastemal type and diffuse anaplasia).

◊ Metastatic sites other than lung were also irradiated; XRT dose varied according to metastatic site.

§ Lung XRT is not required for patients with blastemal type histology who have complete response (ie, resolution of the lung nodule) with initial chemotherapy.

Note that blastemal component more than 2/3rd in SIOP is classified as high risk

16) Testicular torsion

Testicular torsion is a urologic emergency that affects 1 in 4000 males younger than 25 years. The incidence of testicular torsion is bimodal with a peak incidence in the first few days of life and again at puberty (age 13 to 15 years), although it can occur at any age and has been reported in men as old as 78 years.

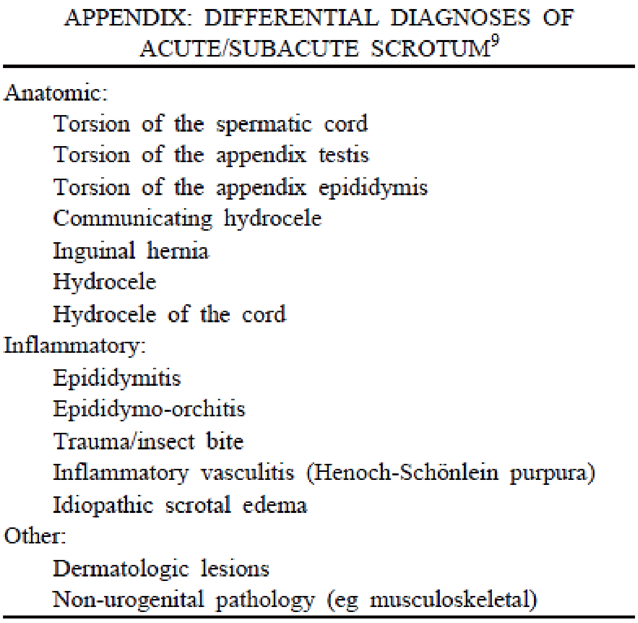
Types

Extravaginal (Perinatal): occurs in the perinatal period before established fixation between the tunica vaginalis and dartos within the scrotum. Large birth weight and difficult delivery may be risk factors.

Intravaginal: is the result of inadequate fixation to the testicular gubernaculum during descent of the testis, thus allowing the testis to rotate freely within the tunica vaginalis. This lack of fixation accounts for the **''bell clapper''** deformity noted in many cases of testicular torsion.
The precipitating factors in those predisposed may be cold temperature, sudden movement, trauma with activation of cremasteric reflex and/or rapid growth of testis at puberty.

Clinical presentation

Acute scrotum in a young male is to be considered as torsion testis unless otherwise proven.



APPENDIX: DIFFERENTIAL DIAGNOSES OF ACUTE/SUBACUTE SCROTUM[9]

Anatomic:
  Torsion of the spermatic cord
  Torsion of the appendix testis
  Torsion of the appendix epididymis
  Communicating hydrocele
  Inguinal hernia
  Hydrocele
  Hydrocele of the cord
Inflammatory:
  Epididymitis
  Epididymo-orchitis
  Trauma/insect bite
  Inflammatory vasculitis (Henoch-Schönlein purpura)
  Idiopathic scrotal edema
Other:
  Dermatologic lesions
  Non-urogenital pathology (eg musculoskeletal)

- On physical examination the **loss of cremasteric reflex** has been shown to be one of the most accurate predictors of torsion.
- A pulled up testis on the affected side on which the pain does not subside on elevation of the testis is also suggestive of torsion.

Management

- **If there is suspicion of torsion, emergent surgical exploration is indicated and should not be delayed to obtain scrotal USG or any other diagnostic test.**
- In cases where the suspicion is low, Doppler USG of scrotum may be obtained – but Doppler USG has only a sensitivity of **63%-90%** in confirming decreased blood flow.

Surgery:
The classic golden hour period for salvage is **6 hours** though the salvage depends on the degree of torsion and the duration.
Consent for orchidectomy has to be taken.

Bilateral intrascrotal fixation (orchiopexy) has to be done as the contralateral side is also at risk for bell clapper deformity. Two point or three point fixation with non absorbable suture material to prevent de-novo torsion in all three planes in future.

Secondary effects

- Testicular torsion may have effects beyond the loss of the torsed testis. Unilateral testicular torsion seriously interferes with subsequent spermatogenesis in about 50% of patients and borderline impairment in another 20%.
- There are several theories to explain **bilateral exocrine failure after unilateral torsion** including **immunological mechanisms, previous episodes of silent intermittent torsion and reflex vasoconstriction**.
- The testis is an immunologically privileged site with a blood-testis barrier composed of tight junctions between Sertoli cells within the seminiferous tubule. Breakdown of this barrier after ischemic damage exposes the antigenic material within the tubule to the immune system resulting in an immunological response that may affect the contralateral testis.

17) Mixed gonadal dysgenesis

- Mixed gonadal dysgenesis is characterized by a **unilateral testis, which is often intra-abdominal, a contralateral streak gonad, and persistent müllerian structures associated with varying degrees of inadequate masculinization**.
- Most patients with mixed gonadal dysgenesis have a **45, XO/46, XY karyotype**, which is probably the result of anaphase lag during mitosis.
- The 45, X/46, XY mosaicism is the most common form of mosaicism involving the Y chromosome.

The **phenotypic spectrum** of patients with XO/XY mosaicism ranges from phenotypic females with Turner syndrome, to those with ambiguous genitalia, to those with normal male genitalia.

- **In the neonatal period, mixed gonadal dysgenesis is the second most common cause of ambiguous genitalia (after CAH) and must be in the differential diagnosis**.
- The majority of these patients have varying degrees of phallic development, a urogenital sinus with labioscrotal fusion, and an undescended testis. In virtually all of these patients, a uterus, vagina, and fallopian tube are present.
- Short stature and associated somatic stigmata are variable features

The mechanism of mixed gonadal dysgenesis is due to lack of local testosterone and MIS effect on one side. Therefore, whereas a dysgenetic or streak gonad is associated with ipsilateral müllerian derivatives (uterus, fallopian tube), a well-differentiated testis with functional Sertoli and Leydig cells will have ipsilateral wolffian but no müllerian ducts. Histologically, the testes lack germinal elements, so **infertility is the rule**.

Associations

- Risk of gonadoblastoma is **15-35%**. Although germ cell tumors occur both in the dysgenetic testes and in the streak gonads of individuals with 46, X/46, XY mosaicism, the risk of tumor is higher in the former.
- Increased risk of Wilms' tumor: in association with Denys Drash syndrome (**progressive renal failure and hypertension – mesangial sclerosis**). In Denys Drash syndrome the risk for gonadoblastoma is **40%.**
- Frasier syndrome (also related WT1 mutations) but **not associated with Wilms**. **Focal segmental glomerusclerosis** form of renal failure (more prolonged than DDS). Risk of gonadoblastoma is **60%**.

Management

The management of mixed gonadal dysgenesis entails:

- **gender assignment**
- **appropriate gonadectomy**
- **proper screening for Wilms tumor**

The likelihood of significant androgen imprinting is greater in association with a better-masculinized phenotype, and this may serve as the best clinical guide.

If the male gender is elected and the testis can be brought to the scrotum, the decision between careful screening for gonadoblastoma (with physical examination and ultrasonography) versus prophylactic gonadectomy and androgen replacement must be made.

18) Persistent Mullerian Duct Syndrome

Persistent müllerian duct syndrome (PMDS), or hernia uteri inguinalis, characteristically describes a group of **patients with a 46, XY karyotype and normal male external genitalia but internal müllerian duct structures.**

Typically, these **phenotypic males** have **unilateral or bilateral undescended testes, bilateral fallopian tubes, a uterus, and an upper vagina draining into a prostatic utricle**. The condition is commonly diagnosed after müllerian tissue is encountered during inguinal herniorrhaphy or orchidopexy.

Three categories:

(1) The majority (60% to 70%) with **bilateral intra-abdominal testes** in a position analogous to ovaries

(2) Smaller group (20% to 30%) in which one testis is found in a hernia sac or scrotum in association with a contralateral inguinal hernia (the classic presentation of **hernia uteri inguinalis**)

(3) The smallest group (10%), in which both testes are located in the same hernia sac (as a result of **transverse testicular ectopia**) along with the fallopian tubes and uterus. Indeed, **PMDS is believed to be etiologically important in transverse testicular ectopia, occurring in 30% to 50% of cases**

Cause: Defective Mullerian Inhibiting Substance (MIS) – either MIS itself or its receptor

Some have defect in the gene for MIS located on chromosome 19p13 and others have a defect in the gene for its type II receptor located on chromosome 12q13 .

Treatment

- The treatment of PMDS is relatively straightforward, in that all patients are phenotypic males who require **orchidopexy**.
- The cases of adult patients with associated testis tumor (most commonly seminoma) probably reflect the increased risk of malignancy in intra-abdominal undescended testes.
- One treatment caveat relates to management of the rudimentary müllerian structures.
- **The vasa deferentia are in close proximity to the uterus and proximal vagina, and historically preservation of the necessary müllerian structures to avoid injury to the vasa was recommended to preserve fertility.**

19) 5 alpha reductase deficiency

5α-Reductase is a microsomal enzyme that catalyzes **the conversion of testosterone to DHT**. The condition is transmitted in an **autosomal recessive** pattern, and only homozygous males are affected. Two 5α-reductase genes have been cloned; they encode different isoenzymes.

- The type 1 isoenzyme, encoded on chromosome 5, is expressed in low levels in the prostate and external genitalia.
- The **type 2 isoenzyme is encoded on chromosome 2 and is expressed in high levels in the prostate and external genitalia**. Male undervirilization caused by 5α-reductase deficiency is secondary to mutations in the type 2 gene.

On presentation individuals with this disorder are neonates with a **46, XY** karyotype and a phenotype that may vary from normal female to markedly **ambiguous genitalia (more common**) to penoscrotal hypospadias to the rare, isolated microphallus.

- Typically the phallus is quite small, appearing as a normal or enlarged clitoris.
- A urogenital sinus is present, with convergence of vaginal and urethral channels, and there is labioscrotal fusion.
- The vaginal pouch is short and blind ending.
- Testes and epididymides are located in the labia, inguinal canals, or abdomen; and the vasa terminate in the blind-ending vaginal pouch.
- At puberty, partial masculinisation occurs with an increase in muscle mass, development of male body habitus, increase in phallic size, and onset of erections.
- Other secondary sexual characteristics, including enlargement of the prostate and hairline recession, do not develop.

Evaluation

On endocrine evaluation these individuals have elevated mean plasma testosterone but low DHT levels. After hCG stimulation, the testosterone-to-DHT ratio increases to greater than 20: 1.Genital skin fibroblast cultures demonstrate diminished to absent 5α-reductase activity. The diagnosis is confirmed by sequencing the entire 5α-reductase type 2 *(SRD5A2)* genes.

The phenotypic characteristics of this disorder have helped to clarify the roles of testosterone and DHT in normal development. **Although DHT appears to be critical for the development of normal external genitalia in utero, testosterone alone appears sufficient for wolffian duct development.**

Management
Studies have shown 56% to 63% of 5α-reductase deficiency patients to undergo gender reversal from **female to male**. The clinician must be open to familial cultural considerations regarding the value of male gender as well as the significance of penile size.
In the setting of **male gender assignment**, cryptorchidism and hypospadias should be surgically corrected. **Fertility is possible**, particularly with the advent of intrauterine insemination.
For some individuals with an **unambiguously female** phenotype or extremely small phallic size, female gender may be assigned. For these patients, gonadectomy should be performed as early as possible and certainly well before puberty to prevent virilization. Estrogen and progestin should be administered at the expected time of puberty. Vaginoplasty and clitoral reduction may be performed within the first year of life in those with a severe defect to provide for normal appearance of the external genitalia and to allay parental anxiety.

20) Megalourethra

Congenital megalourethra is defined as **dilatation of anterior urethra due to absence of development or deficiency of erectile tissue of the penis**.

There are two types:

1) **Fusiform**
2) **Scaphoid**

Fusiform type – There is deficiency of both corpus cavernosum as well as corpus spongiosum. It is thought to result from mesenchymal deficiency in the urethral folds. During voiding the entire phallus dilates.

Scaphoid type – There is deficiency of only corpus spongiosum with preservation of glans and corpus cavernosum. It is thought to result from mesenchymal deficiency in the urethal supportive tissues. During void only the ventral urethra dilates.

- Megalourethra is more commonly associated with **Prune Belly syndrome** than any other syndrome. **Transient in utero obstruction of the junction between the glanular and penile urethra** has been proposed to be the cause.
- Most studies note an **overall poor perinatal outcome** secondary to pulmonary hypoplasia and poor renal function.
- Some may be associated with anorectal malformations.

Management
Surgical reconstruction: Best approached by subcoronal incision and penile degloving. The redundant urethra can be excised and reconstructed over an appropriate sized catheter. As the spongiosum is deficient in both cases, reinforcement with grafts/flaps has been used in isolated case reports.

21) Neourethral coverage in hypospadias repair/Snodgrass repair

Options for urethroplasty in children with hypospadias can be classified as **tubularizations of the urethral plate, skin flaps and grafts**. Throughout the history of surgery for this condition flaps have been most commonly used, but in the past 10 years incision and tubularization of the urethral plate (tubularized incised-plate, TIP) has rapidly gained popularity for correcting distal, proximal and re-operative hypospadias. **TIP potentially simplifies both decision-making and surgical technique, and has a low complication rate with better cosmetic results**. However, careful attention to surgical details and awareness of contraindications to the procedure are needed to achieve optimal results.

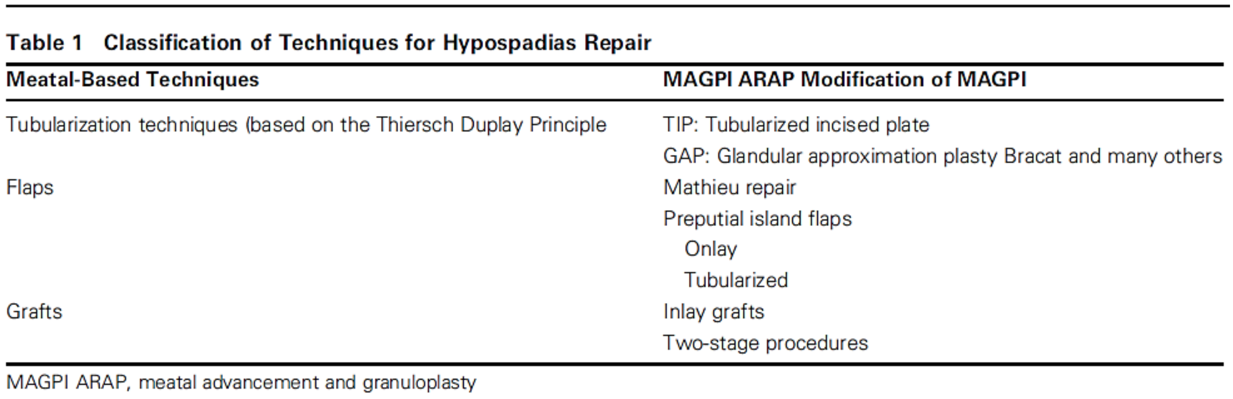


Table 1 Classification of Techniques for Hypospadias Repair

Meatal-Based Techniques	MAGPI ARAP Modification of MAGPI
Tubularization techniques (based on the Thiersch Duplay Principle	TIP: Tubularized incised plate
	GAP: Glandular approximation plasty Bracat and many others
Flaps	Mathieu repair
	Preputial island flaps
	Onlay
	Tubularized
Grafts	Inlay grafts
	Two-stage procedures

MAGPI ARAP, meatal advancement and granuloplasty

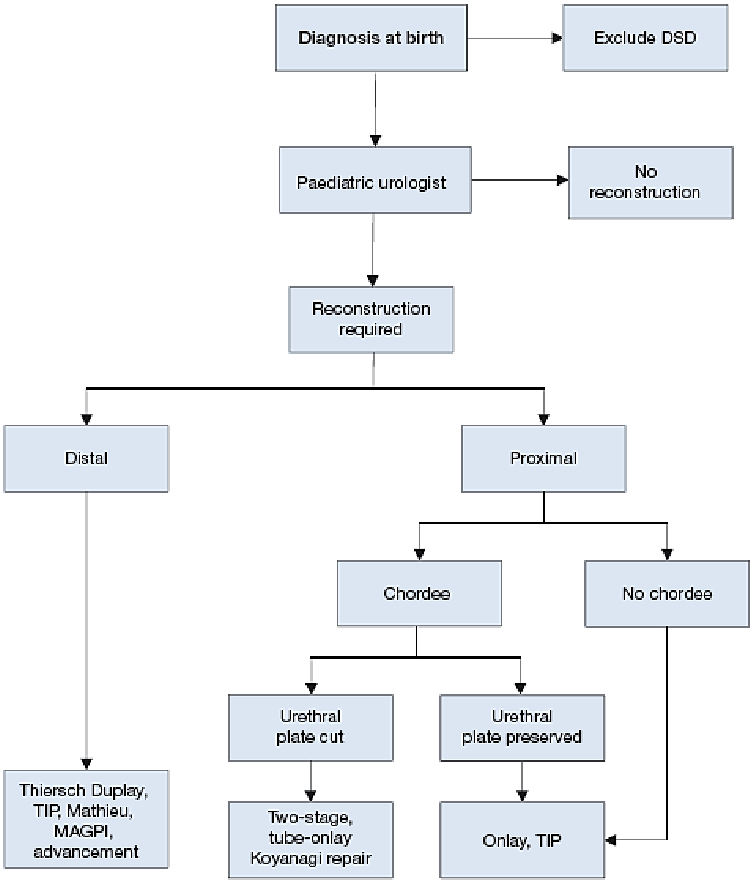
- The mainstay in any hypospadias repair is **preservation of a well vascularised urethral plate striving for functional and cosmetic outcomes**.
- The reason for TIP to gain acceptance was because Snodgrass et al through biopsy showed that the **subepithelial tissue of the urethral plate had well vascularised smooth muscle and collagen** as opposed to the traditional view that in hypospadias the urethral plate was a fibrous band/dysplastic.
- For all procedures use of magnification loupes, fine sutures and surgeon experience have shown to produce better results.

Patient selection:

- Essentially all **patients with midshaft and more distal hypospadias can undergo TIP** of the urethral plate. Those whose plates are **deeply grooved** to near the underlying corpora cavernosa **do not need midline plate incision**, except to remove any transverse webs that might deflect the urinary stream, whereas most with a flat or only moderately grooved plate benefit from the relaxing incision to create an adequately sized neourethra.
- Many cases of proximal hypospadias can also be corrected by TIP, **assuming any associated ventral curvature is straightened without transecting the urethral plate**, and that the **incised plate appears supple**.
- Similarly, TIP is an option for reoperations if the urethral plate has not been excised previously and still appears healthy without gross scars.

The following two diagrams provide management algorithms for management of hypospadias:

Hypospadias management algorithm



The timing of repair is **6-18 months**

DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

Few names to remember would be:

1) **Onlay**:
    a. Ducketts' transverse prepucial island flap
    b. Asopa's inner prepucial onlay/tubularised flap
    c. Koyanagi-Hayasha prepucial onlay– single stage flap

2) **Two stage repair** :
    a. Brakka's repair – prepucial graft/buccal mucosa/posterior auricular FTSG
    b. Byars' prepucial flap for two stage repair

3) **Distal repair**:
    a. GAP – Glandular approximation plasty (Zaontz, Bracat)

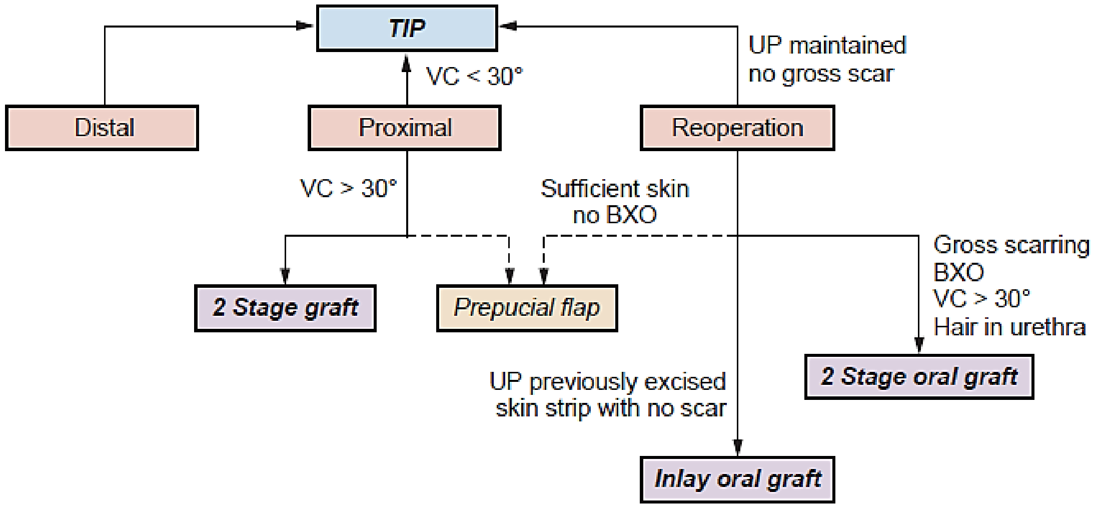
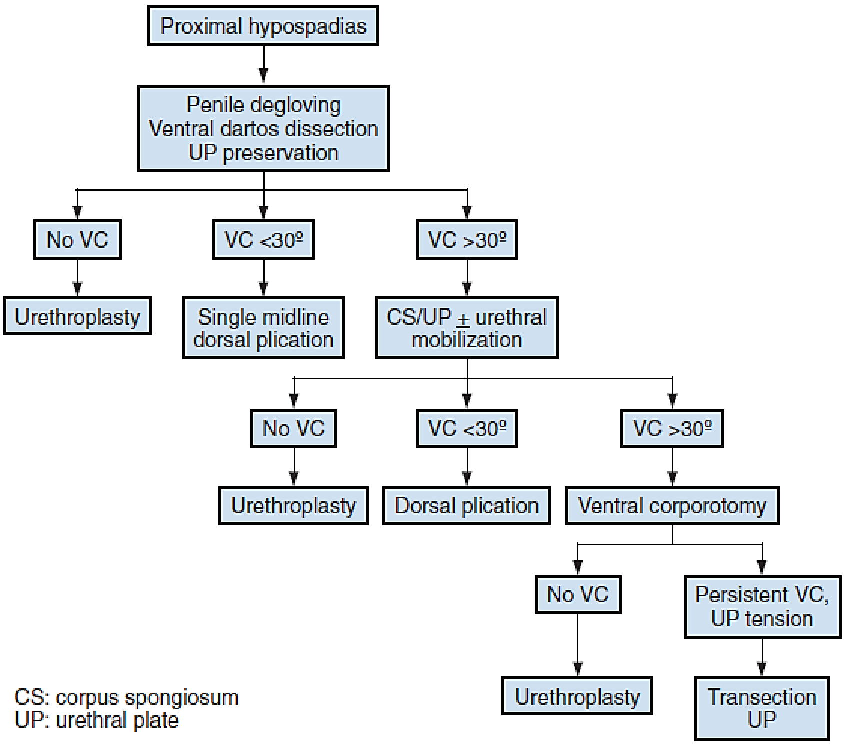


Figure 147-7. **Algorithm for hypospadias urethroplasty. BXO, balanitis xerotica obliterans; TIP, tubularized incised plate; UP, urethral plate; VC, ventral curvature.**

The management of ventral curvature is as follows:



CS: corpus spongiosum
UP: urethral plate

Outcomes and complications:

Glans size <14mm, proximal meatal location, lower surgeon volume and reoperation are independent risk factors for increase in complications.

The complications include: **Fistula formation, stricture, diverticulum, recurrent curvature, glans dehiscence and meatal stenosis**.

The overall complication rate with current techniques for distal hypspadias is **less than 10%.**

For proximal hypospadias is about 25% and for redo/two stage procedures variable (28-68%).

All procedures (including Snodgrass TIP) have usually well preserved sexual function.

22) Circumcision and its complications

Circumcision is one of the oldest urologic surgeries dating back to more than 6000 years – evidence from Egyptian mummies.

American Association of Paediatrics (AAP) in 1989 concluded "Newborn circumcision has potential medical benefits and advantages as well as disadvantages. When circumcision is being considered, the benefits and risks should be explained to the parents and informed consent obtained". The AAP ***does not*** endorse routine circumcision.

Local anesthesia is recommended for neonatal circumcision.

Indications (Newborn and adult)

I. Primary phimosis (persists in less than 1% beyond 27 years, >90% disappears by 3 years)
II. Secondary phimosis (BXO, forceful retraction, balanoposthitis due to diabetes)
III. Large burden of genital warts
IV. Potential preventive role – for HPV related penile and cervical cancer, HIV/AIDS and STIs (Syphilis, HSV2 and chancroid)
V. Potential role to prevent and reduce infant UTIs
VI. Ritualistic purposes – religious.

Contraindications

Hypospadias, penile curvature, dorsal hood deformity, buried penis, webbed penis

Techniques:

I. Neonate – Gomco clamp, Mogen clamp, Plastibell clamp
II. Newborn and Adult :
    a. Dorsal slit – especially in phimosis and paraphimosis
    b. Sleeve method
    c. Bipolar diathermy scissors – potential less bleeding
    d. Guillotine technique
    e. Newer technique – Use hemostatic clamps at 10'o clock, 2'o clock and 6'o clock to crush skin. Cut the three wings separately and suture

In all above local anaesthesia in the form of dorsal nerve block and ring block may be used.

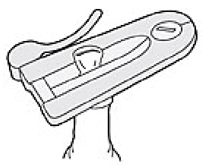


FIGURE 1:

THE MOGEN CLAMP

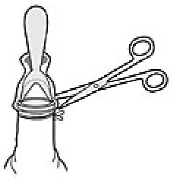


FIGURE 2:

THE PLASTIBELL

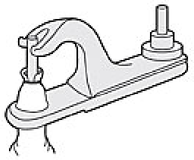
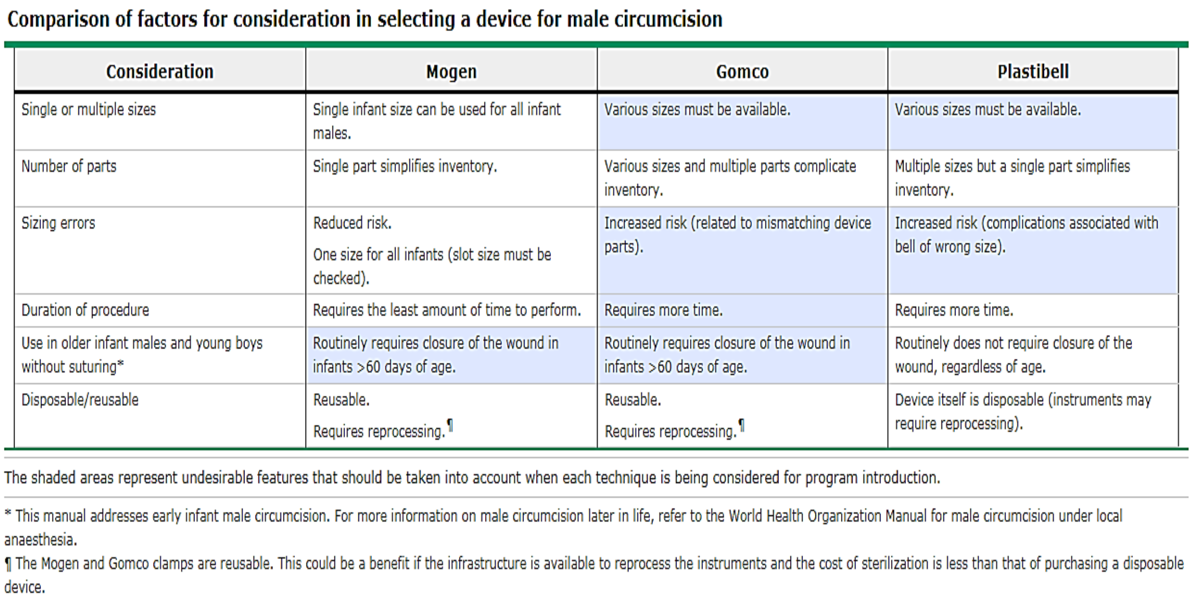


FIGURE 3:

THE GOMCO CLAMP



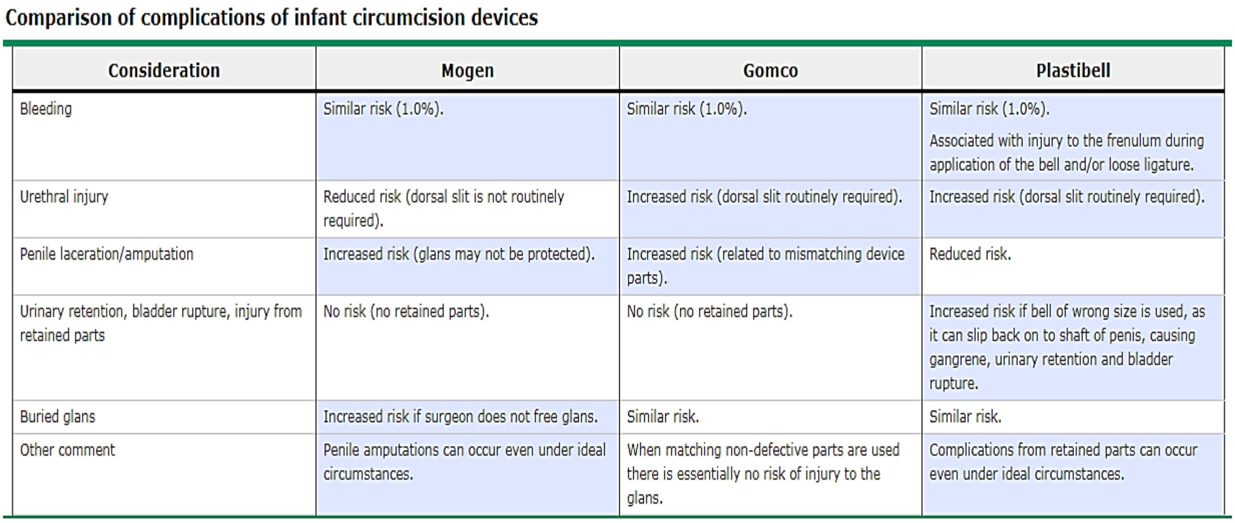
Comparison of factors for consideration in selecting a device for male circumcision

Consideration	Mogen	Gomco	Plastibell
Single or multiple sizes	Single infant size can be used for all infant males.	Various sizes must be available.	Various sizes must be available.
Number of parts	Single part simplifies inventory.	Various sizes and multiple parts complicate inventory.	Multiple sizes but a single part simplifies inventory.
Sizing errors	Reduced risk. One size for all infants (slot size must be checked).	Increased risk (related to mismatching device parts).	Increased risk (complications associated with bell of wrong size).
Duration of procedure	Requires the least amount of time to perform.	Requires more time.	Requires more time.
Use in older infant males and young boys without suturing*	Routinely requires closure of the wound in infants >60 days of age.	Routinely requires closure of the wound in infants >60 days of age.	Routinely does not require closure of the wound, regardless of age.
Disposable/reusable	Reusable. Requires reprocessing.¶	Reusable. Requires reprocessing.¶	Device itself is disposable (instruments may require reprocessing).

The shaded areas represent undesirable features that should be taken into account when each technique is being considered for program introduction.

* This manual addresses early infant male circumcision. For more information on male circumcision later in life, refer to the World Health Organization Manual for male circumcision under local anaesthesia.

¶ The Mogen and Gomco clamps are reusable. This could be a benefit if the infrastructure is available to reprocess the instruments and the cost of sterilization is less than that of purchasing a disposable device.



Comparison of complications of infant circumcision devices

Consideration	Mogen	Gomco	Plastibell
Bleeding	Similar risk (1.0%).	Similar risk (1.0%).	Similar risk (1.0%). Associated with injury to the frenulum during application of the bell and/or loose ligature.
Urethral injury	Reduced risk (dorsal slit is not routinely required).	Increased risk (dorsal slit routinely required).	Increased risk (dorsal slit routinely required).
Penile laceration/amputation	Increased risk (glans may not be protected).	Increased risk (related to mismatching device parts).	Reduced risk.
Urinary retention, bladder rupture, injury from retained parts	No risk (no retained parts).	No risk (no retained parts).	Increased risk if bell of wrong size is used, as it can slip back on to shaft of penis, causing gangrene, urinary retention and bladder rupture.
Buried glans	Increased risk if surgeon does not free glans.	Similar risk.	Similar risk.
Other comment	Penile amputations can occur even under ideal circumstances.	When matching non-defective parts are used there is essentially no risk of injury to the glans.	Complications from retained parts can occur even under ideal circumstances.

Complications The overall complication rate of circumcision is **0.2-6%.**

1) Bleeding and infection are the most common
2) Wound dehiscence
3) Glandular adhesions and skin bridges
4) Penile skin complications – penile chordee, torsion, lateral deviation, trapped penis
5) Meatal stenosis – occurs almost only after circumcision in infancy.
6) Penile and glans trauma.
7) Anaesthesia related – hematoma, intravascular injection.

Long term consequences: Conflicting evidence about decreases glans sensitivity and sexual function.

HIV/AIDS and circumcision

Three RCTs in Orange farm, South Africa ; Rakai, Uganda and Kisumu, Kenya (all three prematurely stopped due to unequivocal benefit)have proven benefit of circumcision in decreasing HIV/AIDS in heterosexual men in Africa.

Probable mechanism: Glans and penile shaft skin are more keratinized than inner prepucial skin. Inner prepucial skin also has high amount of Langerhans cells. The superficial, poorly protected Langerhans' cells on the inner prepuce offer an anatomical explanation for the risk reduction in infection observed after circumcision.

23) Female epispadias

Rare congenital anomaly: **1:484,000** female patients.

Davis classification:

a) **Vesicular** epispadias- Least severe – urethral orifice appears patulous only but relation to clitoris altered.
b) **Subsymphysea**l epispadias - Intermediate – urethra is split dorsally along most of the length.
c) **Retrosymphyseal** epispadias - Most severe – Entire length of urethra split dorsally including sphincteric mechanism rendering patient incontinent.

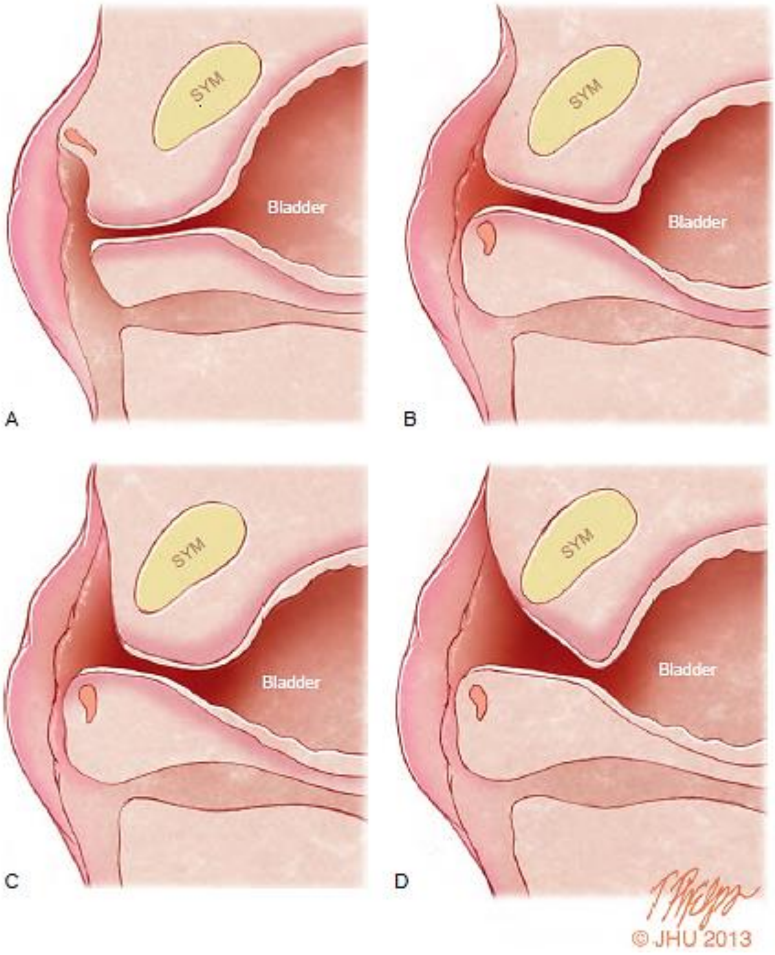


Figure 139-28. A, Normal female anatomy. B, Vesicular epispadias—urethra mainly normal but relation to clitoris altered. C, Subsymphyseal epispadias—defect in anterior wall of urethra for about one half its length. D, Retrosymphyseal epispadias—defect in anterior wall of entire urethra. Sphincter is usually involved. SYM, symphysis. (Used with permission of Brady Urological Institute.)

Genital defect:

- Bifid clitoris, mons depressed and coated by smooth glabrous skin. Labia minora poorly developed and terminate at the corresponding half of the clitoris. On minimally separating the labia, the epispadic urethra is visible.
- The vagina and internal genitalia are usually normal. Because the external appearance changes may be minimal, some children are identified only because of persistent incontinence.

Associated anomalies:

VUR: 30-75%. Because there is no outlet resistance the bladder is usually small and the wall is thin. But after urethral reconstruction bladder develops acceptable capcity for potential later bladder neck reconstruction.

Surgical objectives:

a) Urinary continence
b) Preservation of upper tracts
c) Reconstruction of functional and cosmetically acceptable external genitalia

Operative techniques:

Steps include urethroplasty with genitoplasty are

a) Excision of the glabrous skin
b) Tapering of the urethra
c) Reconstruction of the urethra over a catheter
d) Reconstructio of labia and clitoris
e) Second layer of mons closure
f) Creation of clitoral hood

Surgical results:

Urethroplasty and bladder neck reconstruction may be performed at **same sitting or staged**. By doing staged procedure, the bladder capacity may improve further with time.

About 85% women achieve urinary continence (who had adequate bladder capcity). If the bladder capacity is poor patient may need CIC in post op period and later augmentation cystoplasty.

24) Evaluation and management of bilateral undescended testes in a postpubertal boy

- The incidence of bilateral UDT is **20-30%** of all UDTs.

- The possibilities in a bilateral UDT include bilateral intraabdominal testes, bilateral vanishing testes, bilateral anorchia or a combination of these. Bilateral intraabdominal testes are almost **20 times** more common than bilateral anorchia.
- If a bilateral UDT is associated with a proximal hypospadias, features of ambiguous genitalia or scrotal hyperpigmentation evaluation for **disorders of sexual differentiation (DSD)** has to be done (if already not done till presentation). This would include karyotyping, imaging and serum electrolytes (to rule out congenital adrenal hyperplasia)
- Evaluation of hormonal markers such as **LH, FSH, Mullerian Inhibiting Substance (MIS) and Inhibin B** may provide a clue to the presence or absence of testicular tissue, however rarely do they change the further course which is exploration.

The differences in the post-pubertal scenario are:

a) **Increased risk of malignancy – which remains high even after orchiopexy in a post pubertal setting**
b) **Fertility issues** – affected by alterations in spermatogenesis and endocrine function

The use of imaging in undescended testes is not of much use. Ultrasound has an overall sensitivity and specificity of **45% and 78%** respectively to localise UDT**.** It may be used if there is high suspicion of DSD to rule out Mullerian structures and also in an obese patient when palpation of the inguinal region/scrotum may be difficult. Other imaging modalities such as CT scan and MRI are also not very contributory. MR angiography has been shown in few studies to help identify testicular vessels in bilateral UDT but is not routinely recommended.

The further definitive management is surgical exploration and proceed further depending on intraoperative findings.

In view of delayed presentation (post pubertal), the **patient and family has to be counselled about possibility of bilateral orchiectomy, need for lifelong testosterone supplementation and the risks for malignancy and decresed fertility (even with orchiopexy**).

The following algorithm summarizes the management of UDT in post pubertal setting:

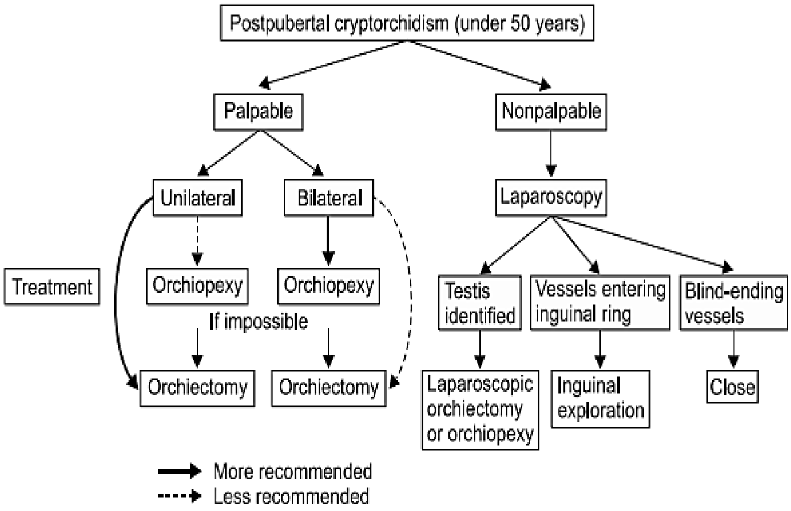


Fig. 1. Algorithm for the optimal individual treatment of postpubertal cryptorchidism.

For intraabdominal testes, orchiopexy can be done using Fowler Stephens procedure in a single stage or two stages.

Post operative follow up if orchiopexy will include monthly self examination of the tested to rule out malignancy and in case of bilateral orchiectomy lifelong testosterone supplementation.

25) Role of imaging in cryptoorchidism

Imaging is **usually not helpful** in the diagnosis and management of cryptoorchidism. **Diagnostic laparoscopy has nearly 100%** sensitivity and specificity for identifying the UDT and also offers the option for simultaneous treatment and is hence the preferred diagnostic modality.

Ultrasound has a sensitivity and specificity of **45% and 78%** respectively to detect undescended testes. It may be used to evaluate the Mullerian structures in **suspected DSD** cases. Also in **obese** patients in whom palpation may be difficult it may confirm the absence of inguinal/scrotal testes. Ultrasound may also play a role in the setting of **reoperation/prior inguinal or scrotal surgery** where palpation may not be possible or accurate.

Studies have shown better accuracy of USG in detecting UDTs near the internal ring or in the inguinal canal however the accuracy to detect intrabdominal testes is very low.

Similarly CT scan and MRI also have limited role in evaluation of UDT. CT scan has additional radiation exposure also.

MRI has greater sensitivity and specificity than USG but is limited by availability and cost. Further in a younger patient sedation and anaesthesia may be required.

Few studies have shown **MR angiography** to be useful in suspected vanishing testes to identify testicular vessels.

One other indication of MRI may be the identification of an **ectopic testis not identified** on laparoscopy.

To summarize imaging may play a role in the following scenarios:

a) Suspected DSD
b) Obese patients
c) Reoperation/prior surgery
d) Post laparoscopy is testes not identified and ectopic testis suspected

VUR – a) Patho-physiology and management. B) Classification of VUR. C) STING. D) Current status of anti-reflux surgery

Pathophysiology

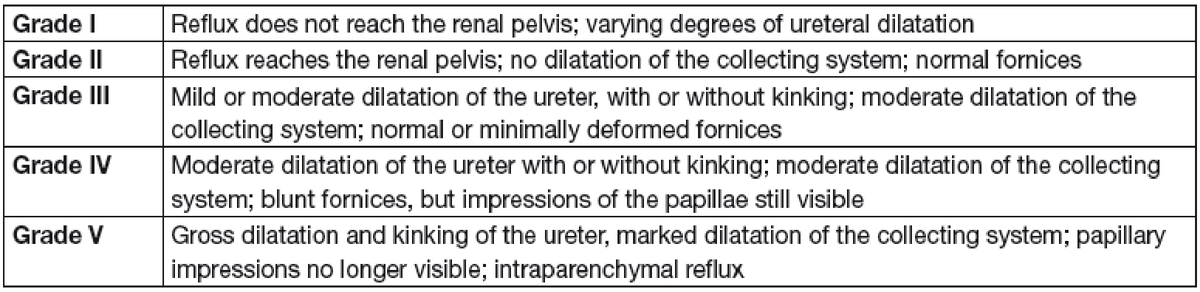
Normal antegrade flow of urine across the VUJ and prevention of retrograde flow into the ureter during void is a balance between several factors including functional integrity of the ureter, anatomical composition of the VUJ and functional dynamic of the bladder.

The intramural portion of the ureter travels within the detrusor muscle as it traverses the bladder wall. The intramural ureter remains passively compressed by the bladder wall during bladder filling, preventing urine from entering the ureter. **Adequate intramural length and ureteral fixation** between extravesical and intravesical points are required to create the antireflux mechanism. Paquin's studies showed a **5:1 ratio** between ureteral diameter and length of the tunnel to prevent reflux.

Any alteration in the above mechanisms can lead to vesicoureteral reflux.

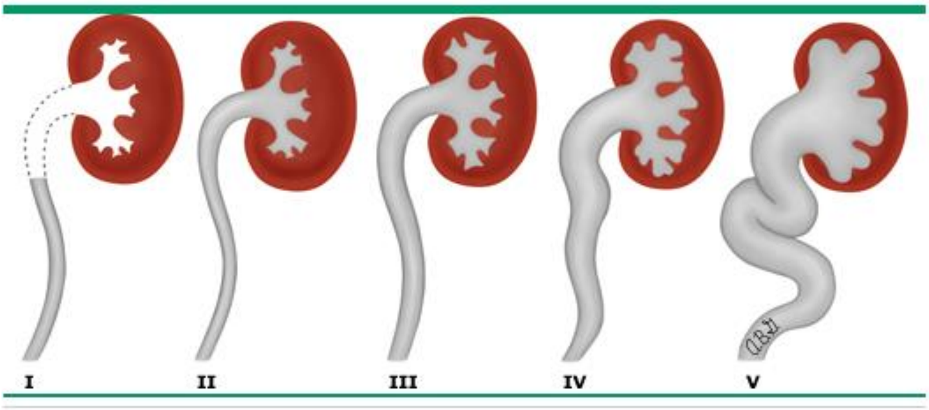
Classification

Classification of VUR: (International Reflux Study Group)



Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

International classification of vesicoureteral reflux (VUR)



Management of VUR:

All children with febrile UTI/symptomatic UTI suspected to have reflux must be evaluated for associated bowel bladder dysfunction (**BBD**) – symptoms of urgency, urge incontinence, hesitancy, incomplete emptying, constipation and fecal soiling.

The factors that need to be assessed during evaluation that will have a bearing on the management include:

a) Age at presentation, gender
b) Clinical presentation – symptomatic UTI/febrile UTI and clinical course
c) Associated BBD/toiled trained?
d) Grade of the reflux
e) Status of the kidney

The evaluation of any patient suspected to have VUR should include assessment of renal status, height, weight, growth and blood pressure.

Urinalysis and urine c/s should also be performed in all. If there is proteinuria on urinalysis urine protein: urine creatinine ratio may be obtained. Serum creatinine and estimated GFR is especially indicated in bilateral disease/solitary kidney/parenchymal dysfunction.

The imaging modalities used for evaluation of VUR include: Ultrasound, VCUG/RNC (Radionucleotide cystogram) and DMSA renal scan.

The indications for VCUG include:

a) First febrile UTI/symptomatic UTI in an infant/not toilet trained child
b) Any age with first febrile UTI if :
    a. Abnormality on ultrasound
    b. >39 degree Celsius fever with significant E.Coli in urine
    c. Poor growth/CKD features/hypertension suspected to be due to reflux
    d. Poor compliance patient in whom follow up may be compromised
    e. Parent preference
c) Any age recurrent febrile/symptomatic UTI

VCUG still remains the gold standard for the diagnosis for VUR as it provides anatomic details of the bladder, bladder outlet and grade of reflux. Concerns with VCUG include invasiveness of the procedure and radiation exposure.

Top down approach: To address the concerns of VCUG a top-down approach was proposed where upfront DMSA scan is done. It is non invasive and avoids radiation exposure. It may miss 5-30% of VUR however it also avoids VCUG in more than 50%.

Screening of family members: There is increases prevalence of VUR in **siblings (27%)** and **off-springs (34%).** So though the data is conflicting sibling screening(USG, VCUG) may be offered to sibling/offspring who is a male, less than 5 years (pre-toilet training when risk of UTI is higher), male and female with h/o BBD or symptomatic/febrile UTI or when you expect the compliance of the family to be poor.

Natural history and course of VUR:

- About **80% of grade I and II** reflux **spontaneously** resolve while **only 30-50% grade III-V** reflux spontaneously resolve. Higher grade reflux and bilateral reflux resolve spontaneously less often.
- **Recurrent UTI**s occur in about 23% of grade III/IV reflux compared to 14% of grade I/II reflux (RIVUR data). Febrile UTI at presentation and presence of associated BBD are at highest risk for recurrent UTIs.

Loss of renal parenchyma is attributed to:

a) Acquired renal scarring due to reflux related pyelonephritis
b) Abnormal development due to congenital renal hypodysplasia.

Parenchymal changes may be seen in as high as 10-40% patients with symptomatic UTIs and around 10-20% of these progresses to hypertension and ESRD.

Contribution of the two mechanisms to renal parenchymal loss may be variable and treatment with antibiotics alone to make urine sterile may not prevent the dysplastic kidney from progressing to scarring/dysfunction.

Goals of treatment:

a) Prevent recurrent UTIs/pyelonephritis
b) Prevent further renal damage
c) Minimize morbidity of treatment and follow up
d) Identify and treat BBD

The treatment options include:

1) Watchful waiting with surveillance
2) Continuous antibiotic prophylaxis
3) Surgery
    a. Open surgery
    b. Endoscopic surgery

Antibiotic prophylaxis is recommended by few studies for all patients.

The indications for antibiotic prophylaxis include:

a) All patients with grade III/IV/V reflux
b) Grade I/II reflux who are not toilet trained or those who are toilet trained but have BBD

RIVUR study (Randomized intervention in VUR)

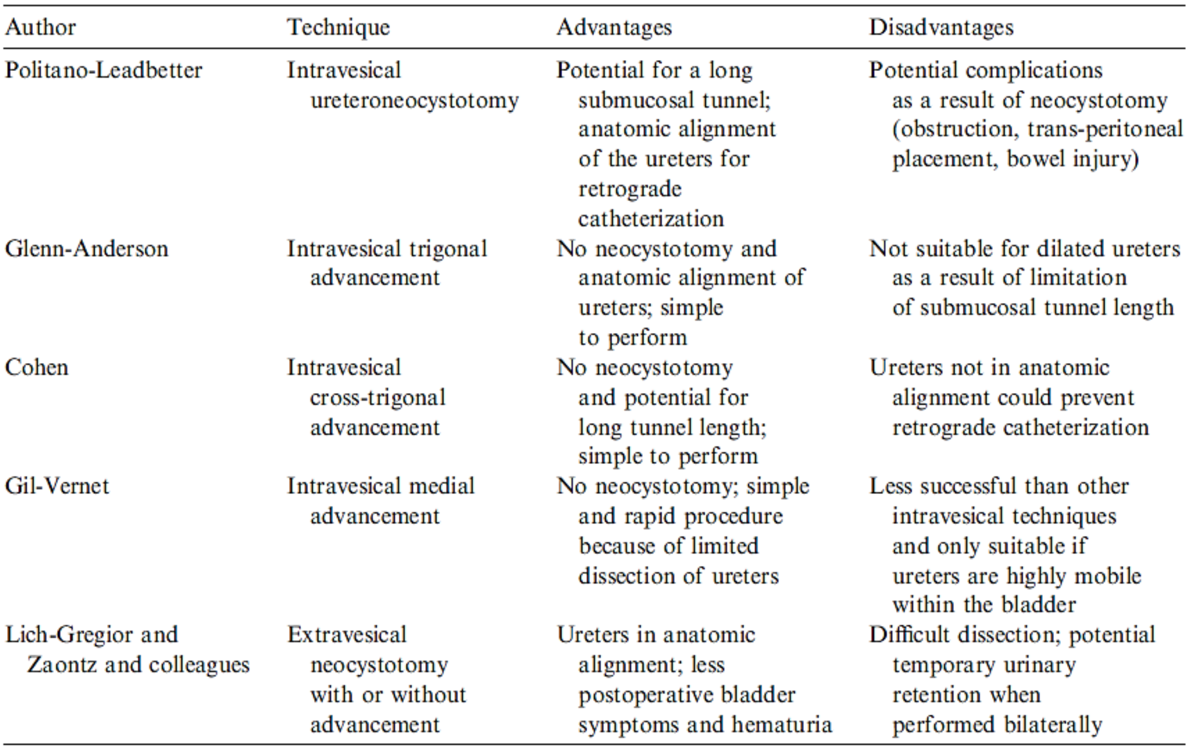
Double blinded, multi-centre RCT. N=607, age =2 months to 72 months, symptomatic/febrile UTI children. Intervention: Placebo versus TMP-SMZ 2mg/kg for 2 years. Primary end point was recurrent UTI. Secondary end point: renal scarring, antibiotic resistance and treatment failure.

There was a 50% reduction in the incidence of recurrent UTI in the antibiotic arm. The difference was most pronounced in the febrile UTI at presentation group and associated BBD group. There was no difference in the renal scarring. The antibiotic resistance to E.Coli during recurrent UTI was higher in the antibiotic group (19% vs 63%).

Indications for surgery (Current status of anti-reflux surgery)

1) Breakthrough UTIs during surveillance
2) Failure of medical treatment
    a. Non compliance
    b. Complications to antibiotics
    c. Deterioration of renal function
    d. Patient preference
3) Associated anatomic abnormalities that require surgery – ureteral obstruction, ureteric orifice opening into diverticulum or very widely patulous orifice.
4) Grade IV/V reflux that persist after more than 2-3 years on medical treatment
5) Girls who have attained full somatic growth at puberty and continue to have significant reflux

The various open surgeries and their pros and cons are summarized below. Overall open surgery has a very high success rate of **95-98%.** In many studies open surgery is better than minimally invasive procedures such as laparoscopy and robotic in terms of length of surgery, complications and success.



Author	Technique	Advantages	Disadvantages
Politano-Leadbetter	Intravesical ureteroneocystotomy	Potential for a long submucosal tunnel; anatomic alignment of the ureters for retrograde catheterization	Potential complications as a result of neocystotomy (obstruction, trans-peritoneal placement, bowel injury)
Glenn-Anderson	Intravesical trigonal advancement	No neocystotomy and anatomic alignment of ureters; simple to perform	Not suitable for dilated ureters as a result of limitation of submucosal tunnel length
Cohen	Intravesical cross-trigonal advancement	No neocystotomy and potential for long tunnel length; simple to perform	Ureters not in anatomic alignment could prevent retrograde catheterization
Gil-Vernet	Intravesical medial advancement	No neocystotomy; simple and rapid procedure because of limited dissection of ureters	Less successful than other intravesical techniques and only suitable if ureters are highly mobile within the bladder
Lich-Gregior and Zaontz and colleagues	Extravesical neocystotomy with or without advancement	Ureters in anatomic alignment; less postoperative bladder symptoms and hematuria	Difficult dissection; potential temporary urinary retention when performed bilaterally

Complications of open surgery include:

a) Early complications – persistent reflux, contralateral reflux, obstruction
b) Late complication – obstruction, recurrent reflux.

Redo re-implantation may be best approached by combination of extravesical and intravesical mobilization.

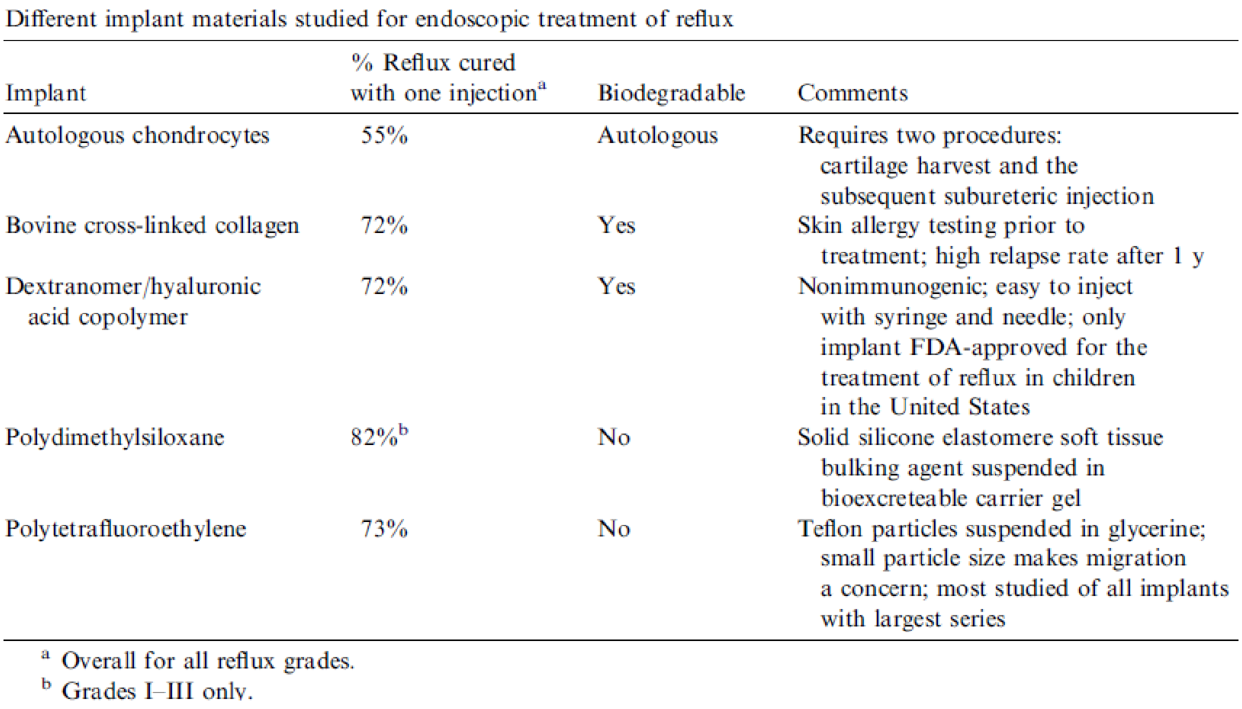
Endoscopic procedure also may be used as salvage for failed open reimplantation.

STING (Subureteric transureteric injection)

Principle: Endoscopic injection of bulking agent beneath the ureteric orifice acts as a buttress that helps to coapt the distal end of the ureter and hence prevents reflux.

Endoscopic procedures may be used in lower grade refluxes in patients who understand the success rate, procedure and complications. It may also be offered to higher grade refluxes based on patient preference after explaining all available options.

Agents used:



Different implant materials studied for endoscopic treatment of reflux

Implant	% Reflux cured with one injection[a]	Biodegradable	Comments
Autologous chondrocytes	55%	Autologous	Requires two procedures: cartilage harvest and the subsequent subureteric injection
Bovine cross-linked collagen	72%	Yes	Skin allergy testing prior to treatment; high relapse rate after 1 y
Dextranomer/hyaluronic acid copolymer	72%	Yes	Nonimmunogenic; easy to inject with syringe and needle; only implant FDA-approved for the treatment of reflux in children in the United States
Polydimethylsiloxane	82%[b]	No	Solid silicone elastomere soft tissue bulking agent suspended in bioexcreteable carrier gel
Polytetrafluoroethylene	73%	No	Teflon particles suspended in glycerine; small particle size makes migration a concern; most studied of all implants with largest series

[a] Overall for all reflux grades.

[b] Grades I–III only.

The ideal agent should be durable, effective, safe, inert, easily injectable, biocompatible, nonantigenic and non-carcinogenic.

Currently Deflux (dextranomer/hyaluronic acid) is most frequently used as PTFE had higher particle migration.

Technique of injection – modified STING (where the agent is injected inside the ureteric canal rather than submucosal) has shown to have better results (92% vs 78%) in one study.

Swedish reflux trial: The overall success rate of STING was **71% at 2 years**. However **about 20% of these recurred at 2 years follow up**. The recurrences were managed with redo-STING successfully in 70-90%.

The failure rate of STING is higher in higher grades of VUR.

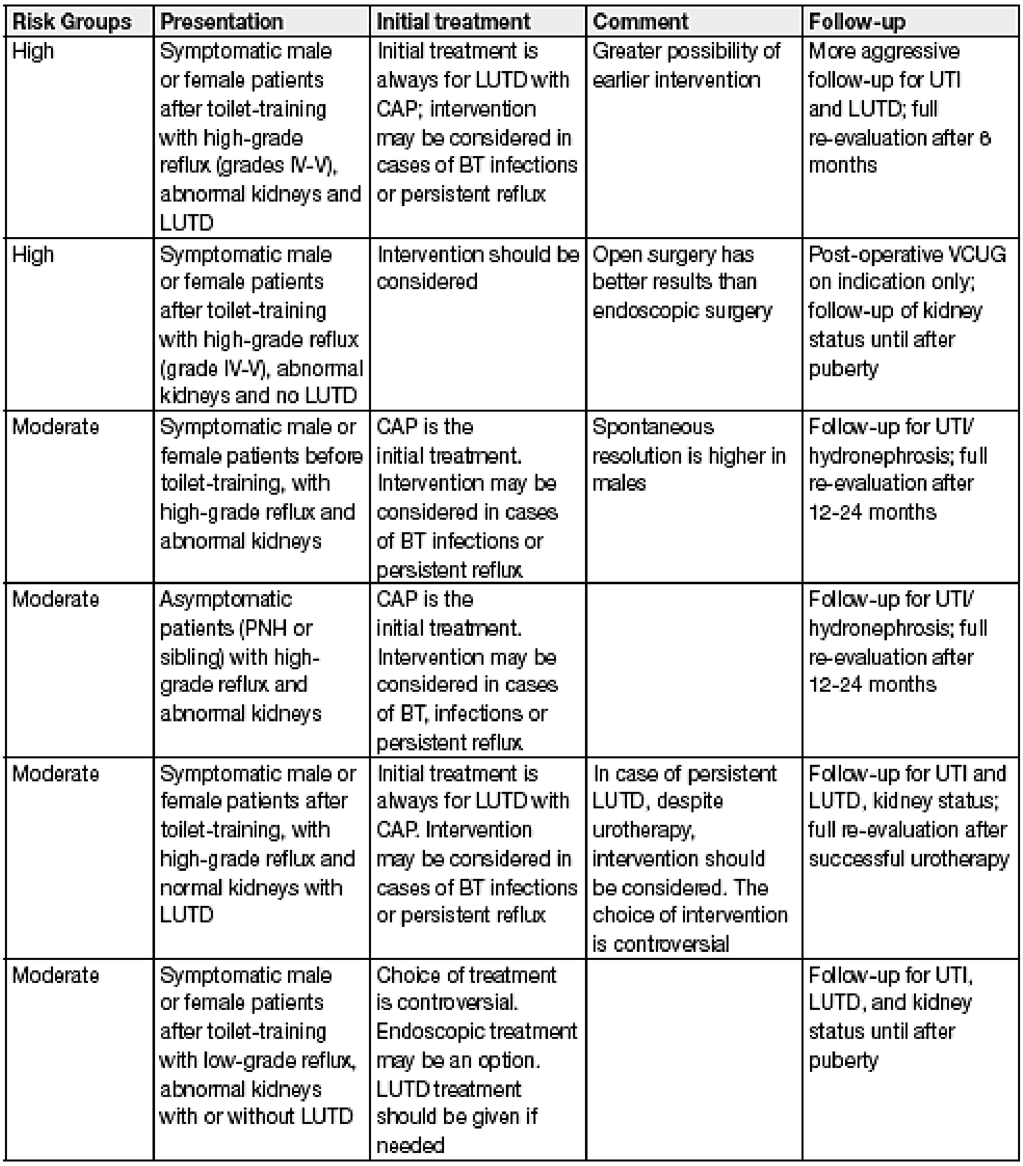
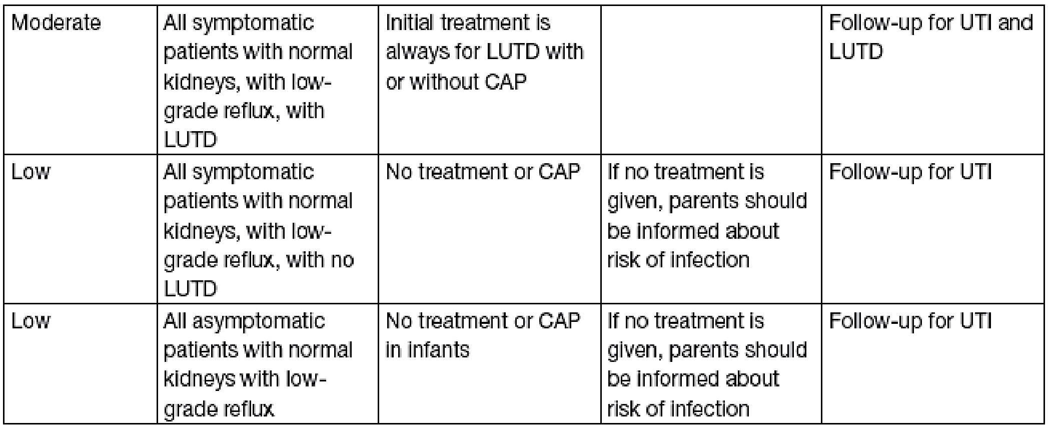
Advantages:

a) Although endoscopic treatment has a little lower success rate, it has the advantage of being a daycare procedure, that is minimally invasive with a low morbidity and a low overall cost
b) Decreased post treatment pain, bladder spasm, infection, and absence of surgical scar.
c) May be used as salvage after failed open surgery.

Complications:

a) Contralateral reflux
b) Obstruction
c) UTI and d) Recurrent reflux

Management according to risk groups

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

2) PUV: A) Ducketts' triad. B) Valve bladder syndrome. C) Urinary diversion in PUV

Ducketts triad

Posterior urethral valves and persistent unilateral reflux after valve resection often have an associated nonfunctioning, dysplastic kidney.

Hoover and Duckett identified the relationship between valves, reflux, and dysplasia, commonly known as **VURD** (Posterior urethral valve, unilateral vesicoureteral reflux, renal dysplasia) syndrome. They noted preserved contralateral renal function in patients with unilateral reflux into a non-refluxing kidney. The proposed mechanism of this protection is that the refluxing collecting system acts as a pressure pop-off.

In the original series VURD was found in 13% of patients and the theory that these children would have better long term renal function was widely accepted. **However, long term studies confirmed that VURD syndrome does not improve renal prognosis**. Only about 30% of kids with VURD had normal creatinine when followed up at 8-10 years of age. The observation that the contralateral normal kidney also carries a high risk for congenital renal damage (dysplasia) implies poorer long term prognosis irrespective of VURD.

Hence VURD should **never be allowed to create a false sense of security** and close follow up like any other PUV cohort is mandatory.

Valve bladder syndrome

In **1982 Mitchell** coined the term valve bladder syndrome after reviewing his experience with eleven PUV patients in whom hydroureteronephrosis and renal function continued to worsen despite no evidence of residual bladder outlet obstruction.

The bladder initially compensates for outlet obstruction by generating high voiding pressures (**Compensated phase**). However the higher volumes of urine due to both increasing urine production as the child grows and due to polyuria caused by a state of nephrogenic diabetic insipidus secondary to evolving renal impairment (both due to dysplasia and obstruction) augments the urine volume entering the bladder. The bladder becomes increasing unable to empty completely and as the post void residuals increase the bladder no longer enjoys periods of complete relaxation (**Decompensated phase**). The detrusor fibres are continuously in a state of partia/complete stretch beginning a cascade of gene expression and phenotypic changes that further impair the contractility of the bladder.

When the bladder does empty partially, the urine stored in the hydronephrotic kidney empties into the bladder once again denying the detrusor periods of relaxation. The impaired contractility and increasing post void residuals then transmit the increasing bladder pressures to the kidney potentially worsening the already impaired renal function.

This "**vicious cycle**" lies at the heart of valve bladder syndrome.

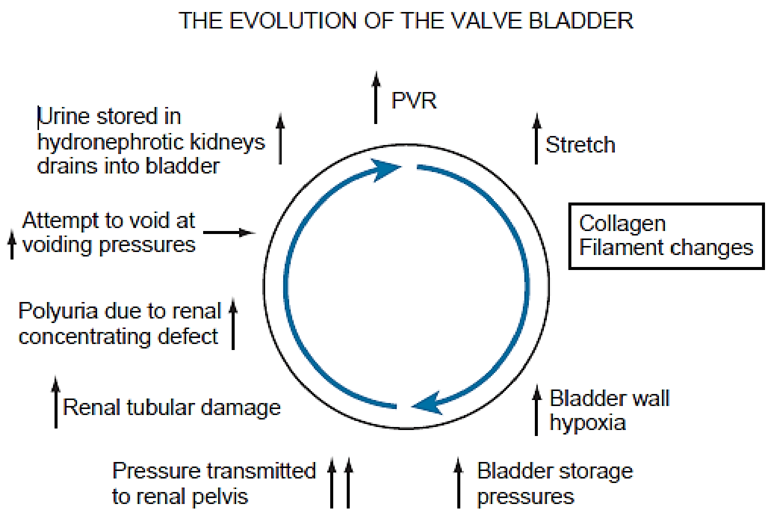

THE EVOLUTION OF THE VALVE BLADDER
↑ PVR
↑ Stretch
Collagen Filament changes
↑ Bladder wall hypoxia
↑ Bladder storage pressures
↑↑ Pressure transmitted to renal pelvis
↑ Renal tubular damage
↑ Polyuria due to renal concentrating defect
↑ Attempt to void at voiding pressures
↑ Urine stored in hydronephrotic kidneys drains into bladder

Figure 141-15. **The valve bladder "vicious cycle." An affected bladder will lead to increasing postvoid residuals (PVR). The sustained stretch will cause increasing collagen deposition and other changes that cause increased pressures to be transmitted to the renal pelvis. Subsequent renal tubular injury causes polyuria and increased volume in the bladder that already empties poorly, and the cycle continues, leading to additive damage.**

In summary the three processes that contribute to the progression of a bladder into a valve bladder in PUV are:

a) Polyuria
b) Poor bladder compliance with high voiding pressures and elevated wall tension
c) Residual urine volume

Related urodynamic details:

Peters described three stages of valve bladder based on urodynamics which Holmadahl and co. described to be three overlapping stages. They are:

A) Detrusor hyperreflexia in infancy and early childhood
B) Decreasing intravesical pressures and improved compliance in childhood
C) Increased capacity with hypocontractility and atony in adolescence (Myogenic failure)

Management of valve bladder

Valve bladder is a continuum of symptoms of bladder dysfunction. Monitoring urine post-void residuals, flow rates and voiding pressures along with renal parameters (RFT and ultrasound) are important. **Timed voiding, double voiding and medications (alpha blockers/anticholinergics depending on voiding pattern**) are used for management. If myogenic failure sets in clean **intermittent catheterisation** may be needed.

Overnight bladder drainage is an important adjunct to break the vicious cycle. It has to be instituted if ureteral dilation does not respond to behavioural modification, if the renal function worsens or child develops recurrent UTIs.

When CIC or overnight bladder drainage is difficult because of elevated bladder neck or sensate urethra, an **appendicovesicostomy** using Mirofanoff's principle is a useful option.

Augmentation cystoplasty is rarely used for valve bladder in the contemporary era. If the bladder is of small capacity, high pressure, thick walled with worsening upper tract refractory to conservative measures (behaviour modification, bladder drainage) augmentation may be used. Ureteral augmentation (using the dilated ureter on the refluxing non functional side) is preferred due to reduced risks of mucous production, acidosis and stones.

Urinary diversion in PUV:

The long-term renal protective benefit of urinary diversion in contemporary practise is questioned because:

- renal biopsies taken at the time of high urinary diversion uniformly show **renal dysplasia**, while the diversion does not seem to protect from renal failure, suggest that renal dysplasia occurring in early fetal development is the primary mediator of renal outcome, rather than any type of complex surgical undertaking (the reversal is also a major undertaking) in the neonate/child.
- Bladder may be exposed to a potentially extended period of **defunctionalization** with attendant risks of impairment in compliance and contractility.

The various urinary diversions (other than attempt at **per urethral** catheterisation at birth) and the scenarios they may be used are as follows:

1) **Suprapubic catheterisation** – If per urethra catheterisation is not possible because of valve not permitting catheter/roomy posterior urethra/other associated urethra anamolies
2) **Vesicostomy** :
   With miniaturization of endoscopic technology vesicostomy is reserved for:
   a) Very low birth weight infant whose urethra cannot accommodate endoscope
   b) Continued impaired renal function, high bladder volumes and upper tract deterioration after valve ablation/per urethral catheterisation.

The argument that vesicostomy defunctionalizes the bladder and leads to decresed compliance in the long term has been refuted by few since a properly constructed vesicostomy allows bladder filling and preserves contractile function because urine must be expulsed out of the stoma albeit at reduced leak point pressures.

The vesicostomy is best seen as a temporary diversion as it does not alter clinical outcomes compared to valve ablation not does it prevent bladder from acting as an adequate reservoir for a renal transplant in future.

3) **Upper tract diversion:**
   May be considered in:
   a) Worsening renal function with increasing upper tract dilation irrespective of complete decompression of lower tract.
   b) In the setting of sepsis.

There are various types of upper tract diversion as shown in the figure below.

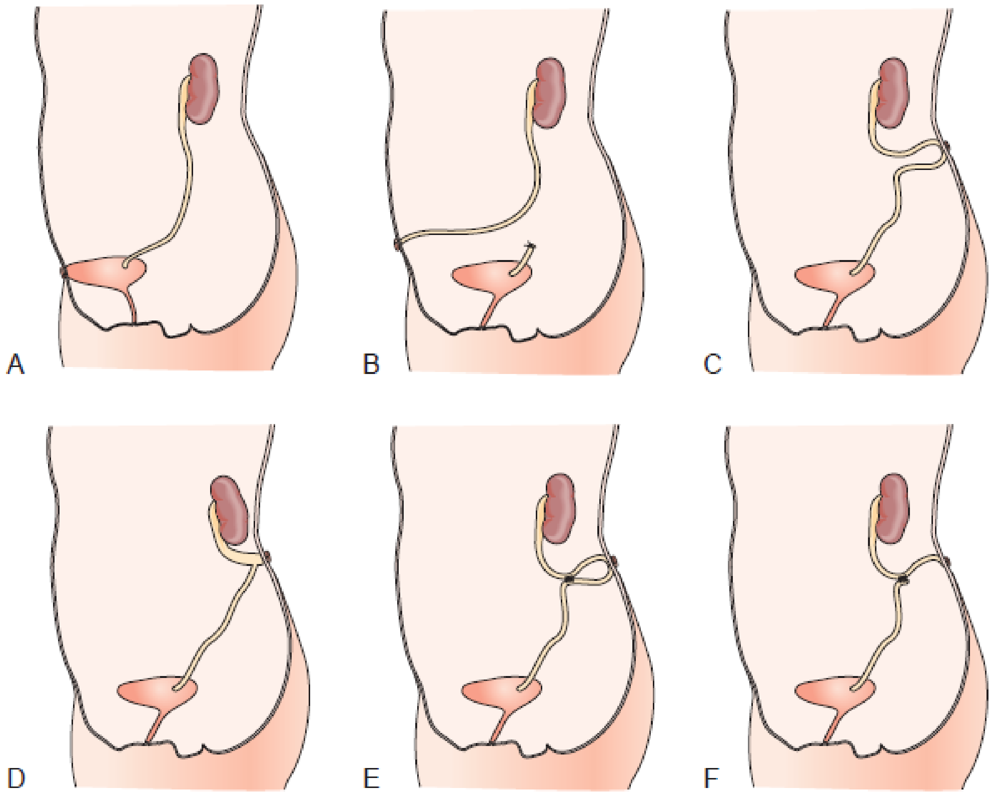


Figure 141-14. The variety of urinary tract diversions useful in posterior urethral valves. A, Vesicostomy. B, Distal ureterostomy. C, Proximal loop ureterostomy. D, Cutaneous pyelostomy. E, Ring ureterostomy. F, Sober Y ureterostomy. (From Glassberg KI, Horowitz M. Urethral valves and other anomalies of the male urethra. In: Belman AB, King LR, Kramer SA, editors. Clinical pediatric urology. 4th ed. London: Martin Dunitz; 2002. p. 899–945.)

4) In valve bladder syndrome, in patients who cannot perform CIC/overnight bladder drainage due to high bladder neck/sensate urethra **appendicovesicostomy** (by Mitrofanoffs principle) may be used as a urinary diversion procedure.

Extrophy – embryology, anatomy, variants and management

Bladder extrophy is complex congenital anomaly that forms a part of the **spectrum** of Extrophy-epispadias complex. Epispadias is the mildest end of the spectrum while cloacal extrophy is the most severe.

The incidence of bladder extrophy is **1 in 10,000 to 1 in 50,000**. More common in males 2.3:1

Offsprings of affected individuals have 1:70 incidences (a **500-time** greater incidence).

Embryology

The theory of embryonic maldevelopment in extrophy held by **Marshall and Muecke** (1968) is that the basic defect is an **abnormal overdevelopment of the cloacal membrane**, which **prevents the medial migration of the mesenchymal tissue and proper lower abdominal wall development**. The **timing** of the rupture of the defective cloacal membrane determines **the variant** of the extrophy-episapdias complex that results.

Anatomy

Bladder extrophy has the following anatomical defects:

a) **Skeletal defects** – Pelvic bone abnormalities such as lateral rotation, pubic diastasis and sacroiliac joint defects.
b) **Pelvic floor defects** – Levator ani group of muscles is positioned more posteriorly
c) **Abdominal wall defects** – The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the extrophy bladder and posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band that represtnts the divergent urogenital diaphragm. Umbilicus is low set. The distance between umbilicus and anus is always foreshortened. Omphaloceles may be rarely seen (more common in Cloacal extrophy). There is frequent occurrence of inguinal hernia (80% in boys and 10% in girls).
d) **Anorectal defects** – Perineum is short and broad. The anus is situated directly behind the urogenital diaphragm. It is displaced anteriorly and corresponds to the posterior limit of the triangular defect. The divergent levator and pelvic floor defects predispose to varying degrees of anal incontinence and prolapsed.
e) **Male Genital defects** – Anterior corporal length is 50% shorter in affected individuals. The prostate and accessory organs are normal. The epispadias is usually associated with dorsal chordee. Most of the cases testes are descended and fertility is not impaired.
f) **Female genital defects** – The vagina is shorter but normal calibre. The vaginal orifice is frequently stenotic and displaced anteriorly. The clitoris is bifid with divergent labia and mons. Fallopian tubes and ovaries are normal.
g) **Urinary defects** – The kidneys are usually normal (may be affected more in cloacal extrophy). Though the bladder is exposed, studies have shown the overall neurophysiology to be normal (the muscarinic receptor distribution and innervations). After closure of bladder extrophy the occurrence of VUR is nearly 100% - these needs to be addressed at time of bladder neck closure.

Extrophy variants

The variants reflect the timing of rupture of the defective cloacal membrane:

1) **Superior vesical fissure variant** – The muscular and skeletal defects are the same however the persistent cloacal membrane ruptures only at the uppermost portion and a superior vesical fistula that actually resembles a vesicostomy results.
2) **Duplicate extrophy** – The urinary tract shows duplication with one of the two being present in the extrophy.
3) **Pseudoextrophy** – No urinary tract abnormality – only muscular and skeletal defects.
4) **Covered extrophy/split symphysis variant** – Thin membrane like skin covers the bladder which is seen in the subcutaneous position.
5)

Management

Antenatal ultrasound reveals

a) Empty bladder/non visualisation of the bladder
b) Infraumbilical anterior wall defect/cystic structure
c) Omphalocele if present
d) Associated anomalies may be identified

If the diagnosis is made prenatal – the parents need to be counselled about the condition.

At time of delivery – the bladder should be preferably covered with adherent transparent dressing to prevent trauma. It may be periodically wetted with sterile saline. Routine use of antibiotics is unnecessary.

Abdominal and pelvic XRAY and ultrasound should be obtained and other teams – orthopaedics, paediatrics and anaesthesia be involved. Rarely preoperative MRI may be obtained to delineate pelvic soft tissue better.

Surgical goals – Preserve renal function, allow adequate bladder storage and function, and provide acceptable cosmesis and function.

Timing of first surgery can be as early as within first 48**-72 hours or be delayed for 4-6 weeks**.

The various surgeries used are:

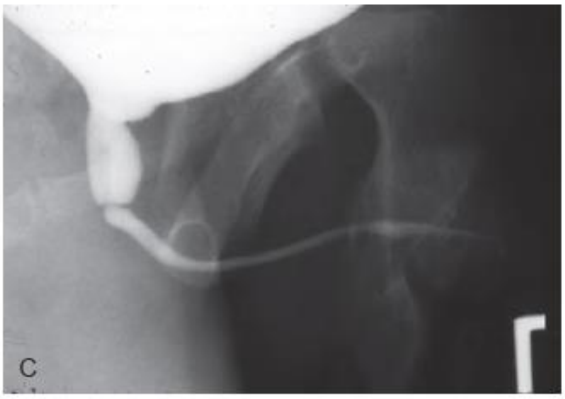
1) **Modern staged repair of bladder extrophy (MSRBE)**: Involves three stages namely bladder closure at birth, epispadias repair between 6-12 months and bladder neck reconstruction at 5 years.
   Pelvic bone osteotomy may be done before bladder closure if the pelvic bones are not malleable or the diastasis is more than 4 cm. In either case, post bladder closure the child needs immobilisation with cast (usually Bryant type traction given) for 2-4 weeks.
2) **Complete primary repair of bladder extrophy (CPRBE):** All three stages performed in one shot. However, in more than 50% cases another surgery for bladder neck reconstruction is required.
3) **Urinary diversion**: Most centres perform one of the above two, rarely urinary diversion (bladder-bowel) or continent catheterisable diversions are peformed.
4) For epispadias repair the surgery commonly performed is modified **Cantwell Ransley** procedure.

   Complications:
   Bladder dehiscence, UTIs, bladder calculi, fistulas, hypospadias are the post op complications.
   In the long term vaginal and rectal prolapsed may develop. And development of malignancy is another long term complication.

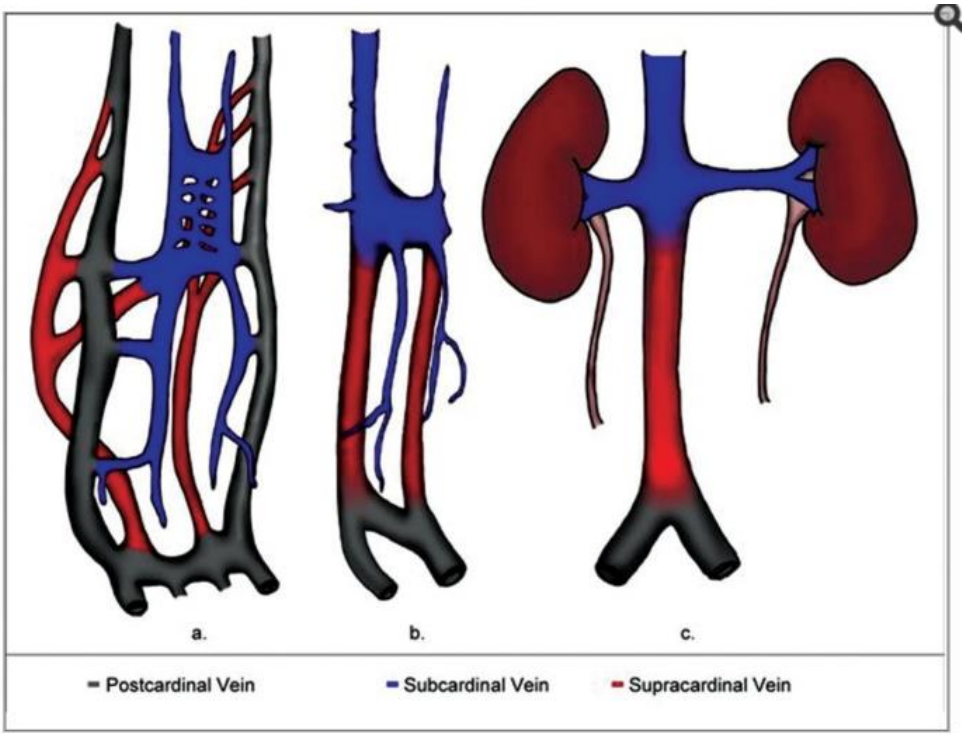
   Outcomes:
   In both the surgical approaches continence is eventually maintained in about 70% (thought the CPRBE may need additional bladder neck procedures.
   Men may have ejaculatory problems but are fertile and about 2/3 rd of female patients can conceive normally.

Some other questions from 2000-2011 (especially odd balls) Wind sock valve

Type 3 PUV is called wind sock valve because of its characteristic appearance on VCUG. Constitutes less than 5%

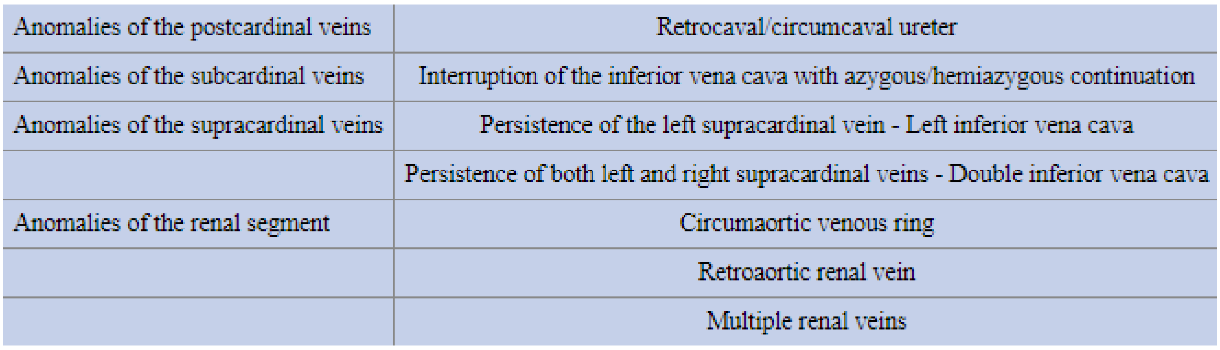


1) IVC embryology, anomalies and significance



Subcardinal and supracardinal veins. Figure 1a demonstrates the three sets of paired veins that develop in the embryo, namely the subcardinal (blue), supracardinal (red) and postcardinal veins (grey). **1b.** The right subcardinal vein becomes dominant. Figure 1b demonstrates regression of the postcardinal veins; the supracardinal veins become dominant infrarenally, while the subcardinal veins become dominant above the renal veins. **1c.** Final structure of the IVC. Figure 1c demonstrates the final composition of the inferior vena cava.

Classification of IVC anomalies



Anomalies of the postcardinal veins	Retrocaval/circumcaval ureter
Anomalies of the subcardinal veins	Interruption of the inferior vena cava with azygous/hemiazygous continuation
Anomalies of the supracardinal veins	Persistence of the left supracardinal vein - Left inferior vena cava
	Persistence of both left and right supracardinal veins - Double inferior vena cava
Anomalies of the renal segment	Circumaortic venous ring
	Retroaortic renal vein
	Multiple renal veins

Anomalies of the IVC or renal veins are rare anatomical variants that result from abnormal development/regression of the fetal venous circulation. With the exception of retrocaval/circumcaval ureters, the majority of patients are asymptomatic and these variants are detected incidentally on CT/MRI. Their presence may have significant implications for surgical procedures, as careful preoprative planning is required. This is particularly the case for procedures such as laparoscopic radical nephrectomy or laparoscopic donor nephrectomy.

2) Embryolgy and types of ureteroceles

CLASSIFICATION —

Ureteroceles are classified as **intravesical** (ie, entirely within the bladder) or **ectopic** (ie, a portion extends beyond the bladder neck into the urethra) . At times, differentiating between intravesical and ectopic ureteroceles may be difficult. Historically, ectopic ureteroceles that inserted beyond the bladder neck into the urethra were **called cecoureteroceles**.

Ureteroceles also may be classified depending upon whether they are associated with either a **single collecting system** (ie, single ureter and kidney) or a **double collecting (duplex) system (complete ureteral duplication).** Approximately 80 percent of ureteroceles are associated with the upper pole of a duplex collecting system, and 60 percent of these are ectopic, whereas intravesical ureteroceles are more common in single systems.

PATHOGENESIS — The underlying pathogenesis is unknown, and it appears that a single unifying theory does not explain how all the different types of ureteroceles are formed . A simple explanation is that ureteroceles can be considered a diverticulum of the distal ureter within the bladder, secondary to a stenotic ureteral orifice. Ureteroceles may be one type of abnormal ureteral insertion at the bladder level, along with pseudoureteroceles and ectopic ureters, which have similar etiologies.

More formal proposed embryologic mechanisms resulting in ureterocele formation include:

●An incomplete breakdown of the ureteral membrane between the ureteral bud and mesonephric duct, resulting in an obstruction that causes the formation of a ureterocele. This mechanism explains the formation of the majority of stenotic ureteroceles, but not those with patulous ureteral orifices in the urethra.
●Obstruction of the ureteral orifice by the bladder neck, because of developmental delay in the timing of the ureteral bud insertion into the bladder.

●Abnormal induction of the bladder trigone development that results in the absence of trigonal musculature in the intravesical portion of ureteroceles.

3) Congenital collecting system abnormalities other than PUJO

1) Calyceal diverticulum
2) Hydrocalicosis – rare cystic dilation of the major calyx with demonstrable connection to pelvis.
3) **Megacalycosis** – Non obstructive enlargement of calyces resulting from malformation of the renal papillae. The calyces may increase in number also (12-20). The renal pelvis and UPJ are normal. The surrounding cortical tissue is normal. The medulla however is underdeveloped. A mild disorder of concentrating ability of urine has been reported.
   Megacalycosis occurs predominantly in males (6:1) and has been found only in whites. Bilateral disease occurs almost exclusively in males while unilateral segmental disease occurs only in females.
   The increased number of calyces may be an aborted response by the branching ureteric buds to transient obstruction when glomeruli start producing urine.
   Long term follow up does not reveal progression of anatomic derangement or functional impairment.
4) Unipapillary kidney
5) Extrarenal calyces
6) Anomalous calyx (**Pseudotumor of the kidney**) – hypertrophied colums of Bertini. Echogenic pattern on USG with normal uptake on renal scan
7) Infundibulopelvic stenosis
8) Pelvis - extrarenal pelvis, bifid pelvis

4) Giggle incontinence (type of voiding dysfunction)

Giggle incontinence — Giggle incontinence, a rare syndrome, refers to urine leakage that occurs only with laughter . Children with giggle incontinence have normal bladder function when the child is not laughing and should be differentiated from urinary leakage with laughter in children who have persistent voiding symptoms when they are not laughing. It occurs almost exclusively in girls and is characterized by large-volume voids.

Although the etiology of giggle incontinence is unclear, one theory suggests that this disorder is mediated by the central nervous system. The proposed mechanism is similar to that of cataplexy, in which an emotional event causes muscle hypotonia .

Treatment of this condition is not well studied. Some experts in the field advocate the use of anticholinergics based upon the assumption that incontinence is related to detrusor instability. Small case series report that methylphenidate was effective in the prevention of these events suggesting a central nervous system etiology . In one small case series, biofeedback to teach the patient to contract the external sphincter was effective in nine patients with giggle incontinence either refractory to medications or whose parents refused pharmacotherapy.

Vaginal voiding — Vaginal voiding or vaginal reflux of urine, is leakage of urine in toilet-trained girls when they stand up after voiding, and is a common cause of daytime urinary leakage in girls . This is due to urine being temporarily trapped in the vagina during micturition. It occurs particularly in girls who urinate with their legs too closely approximated to permit free egress of urine. It is a pattern that can be seen during voiding cystourethrography with refluxing urine appearing within the vaginal vault during voiding.

Girls with this condition may also have irritation of the labia and complain of dysuria as the urine passes over the irritated skin.

Treatment is based upon changing the voiding habits of the child by emphasizing wide abduction of the legs and a forward leaning posture to reduce the likelihood of vaginal reflux of urine. Other helpful tips include sitting backwards on the toilet so that the legs need to straddle the toilet or manually spreading the labia majora while voiding.

5) Mechanism of testicular descent

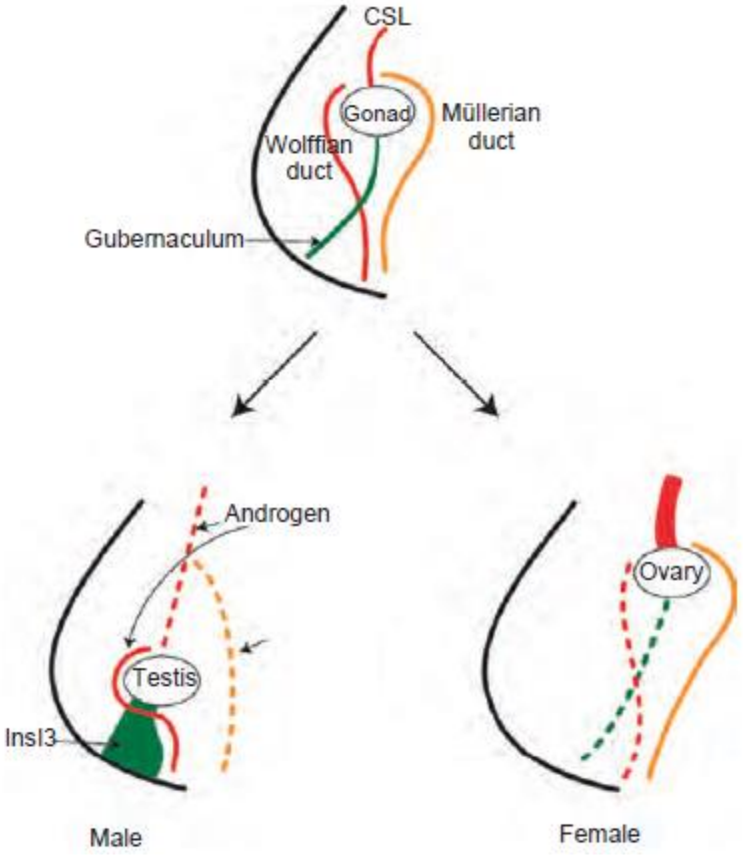


Figure 122-26. **Mechanism of gonadal descent. The undifferentiated gonad is initially located high in the abdomen, anchored by the cranial suspensory ligament (CSL). In males, Insl3 will cause the swelling and enlargement of the gubernaculum to pull the developing testis toward the inguinal region, whereas androgens will cause an involution of CSL. Owing to the action of müllerian-inhibiting substance, müllerian ducts will regress while androgens continue to stimulate the development of wolffian ducts into male genital ductal structures. In females, CSL persists because of the absence of androgens, and the gubernaculum remains thin as a result of the absence of Insl3 activity, thereby keeping the ovary well within the pelvis.**

a) Transabdominal descent – androgen independent – occurs between 2 months – 7months – Gubernacular swelling, CSL regression and action of INSL3
b) Inguinoscrotal descent – androgen dependent (?androgen acts through genitofemoral nerve) – from 7th month – intraabdominal pressure transmitted through processus vaginalis may also play a role.

6) Noonans syndrome

Noonan syndrome — Noonan syndrome is a relatively common autosomal dominant disorder with an estimated incidence of one in 1000 to 2500 live births. Approximately 50 percent of children with Noonan syndrome have a mutation in the PTPN11 gene, mapped to chromosome 12q24.1, which encodes the non-receptor protein tyrosine phosphatase SHP2 . Children with mutations in *PTPN11* have mild growth hormone resistance . Less common mutations have been described in *KRAS*, *SOS1*, and *NRAS* (which, like *PTPN11* mutations, result in upregulation of the RAS-MAP kinase pathway , as well as mutations in *RAF1, RIT1, MAP2K1,* and *BRAF* . Mutations in one these genes are found in approximately 70 percent of individuals with Noonan syndrome. Noonan syndrome and neurofibromatosis type 1 may occur together in patients with certain *NF1* mutations. Some patients with *PTPN11* mutations also have a syndrome that includes giant cell lesions of bone or soft tissues.

Noonan syndrome is characterized by minor facial dysmorphism (hypertelorism, downward eye slant, and low-set ears), proportionate short stature, and heart disease, most often pulmonic stenosis and hypertrophic cardiomyopathy . Other common findings include a short webbed neck, chest deformity (pectus excavatum), cryptorchidism, intellectual disability (mental retardation), bleeding diathesis, and lymphedema. There appears to be a modest association between Noonan syndrome and several types of cancer, including neuroblastoma, acute leukemia, low grade glioma, and embryonic rhabdomyosarcoma

The cardiac manifestations were assessed in an echocardiographic study of 118 patients with Noonan syndrome . A dysplastic pulmonary valve was present in eight patients (7 percent), six of whom had significant stenosis. Among the 110 patients without valve dysplasia, significant pulmonic stenosis was present in 22 (20 percent). Other abnormalities included secundum atrial septal defects, localized anterior septal hypertrophy, and diffuse hypertrophy.

Short stature associated with Noonan syndrome can be treated effectively with growth hormone and is an approved indication by the US Food and Drug Administration (FDA)

7) Hugh Hampton Young

Hugh Hampton Young, MD was born in San Antonio, Texas in 1870. He attended the University of Virginia where in four years he received a bachelors, masters and medical degree by 1894. He returned to San Antonio to begin a surgical practice, but realized his limitations very quickly and decided to go to The Johns Hopkins Hospital for postgraduate education. Working in the surgical dispensary, he eventually obtained a position as a resident on the surgical wards. By 1897, three years after graduating from medical school, Dr. Halsted, the chief of surgery, asked Dr. Young to take charge of the Genitourinary Surgery Division. Thus began the career of the individual who is considered the "Father of American Urology."

Dr. Young remained at Hopkins and developed a number of innovative instruments and techniques. His first new instrument was the "punch" for blind resection of obstructing bladder neck and prostatic tissue, which led to the development of numerous other punches, particularly at the Mayo Clinic where several of his students perfected this instrument. Using the punch on a railroad entrepreneur by the name of James Buchanan "Diamond Jim" Brady, whom he relieved of his obstruction in 1912, convinced Brady to fund the construction and creation of the Brady Urological Institute. There, Dr. Young designed a urological operating table and developed a detailed approach to perform radical perineal prostatectomy which became the standard for prostate cancer surgery (1904). In 1926 Dr. Young published "Young's Practice of Urology." A pioneer in hermaphroditism and related diseases, he published: "Genital Abnormalities, Hermaphroditism, and Related Adrenal Diseases" in 1937. He wrote about mercurochrome as an intravenous antiseptic agent and extensively tested and wrote about sulphanilamide in the treatment of venereal disease. In 1917, he founded *The Journal of Urology®* which he edited until his death in 1945.

Dr. Young created a detailed plan for the training of young urologists; his program became the model for all other training programs in the United States.

Dr. Young was a prolific writer, frequent guest speaker at national and international meetings, researcher, educator and surgeon. Nevertheless, he still found time to pursue numerous other interests in the realm of the arts: seeking funds and land for the creation of a museum in Baltimore, chairing a fund drive to save the symphony house which was on the auction block, promoting legislation for better care and better facilities for "insane asylums," and spearheading the construction of a bridge across the Potomac.

Dr. Young was president of the American Association of Genitourinary Surgeons and of the AUA in 1909, and became president of the International Association of Urology in 1927.

While recuperating from a herpes zoster infection in 1940, Dr. Young dictated his last major book: "Hugh Young: A Surgeon's Autobiography." He died after several heart attacks in 1945 in Baltimore.

8) Urological Society of India

The Urological Society of India (USI) came into existence as 'Urology Section' of the Association of Surgeons of India (ASI) at their Annual Conference in Baroda in December, 1961. At inception a provisional Executive Committee with the late Dr. G.M. Phadke as the Chairman and Dr. B.N. Colabawalla as the Hon.Secretary-cum-Treasurer, were entrusted with the task of framing the rules, enrolling members and ensuring passage through the Governing Body of A.S.I. The membership of the Urology Section, which was later on rechristened as, "The Urological Society of India" was 32, and most of whom were general surgeons along with a handful of trained urologists.

The first department of Urology, free from the shackles of general surgical service probably was at George's Hospital, Bombay in 1961-62 with Dr. B.N. Colabawalla as the Head. Well established centres were soon established at Madras, Vellore. Delhi and Chandigarh under the Chairmanship of Prof.A.Venugopal, Prof. H.S. Bhat, Prof. S.M. Singh and Prof. B.C. Bapna. What followed in the subsequent 3 decades, was the establishment of many such departments all over the country. At present, we have close to 100 centres recognized for M.Ch. Urology training and about equal number of centres recognized by the National Board of Urology for the award of D.N.B.

The Society holds its annual conference usually in the month of January by rotation in the four zones. The annual conference is usually attended by close to 2000 delegates. Apart from scientific deliberations, there is technical exhibition for latest equipment in urology.

The Society has created 4 zonal chapters with the idea of spreading urology to each & every corner of India. Each zonal chapters conducts CME programmes & workshops and zonal annual conference which are attended by 300-400 delegates.

The Society also publishes its own journal, the 'Indian Journal of Urology', and a Newsletter, four times a year. The Indian Journal of Urology is an indexed Journal by the Excerpt Medica and Pubmed (Medline).

The Indian Urology has now come of age and the membership has now crossed 3100. We have ntered the new millennium with plenty of hope and promise from our younger colleagues, who will take us to even greater heights.

Lymphatic drainage of the penis and management of lymph nodes in carcinoma penis

Lymphatic drainage of the penis:

Lymphatic drainage of the penis parallels venous drainage – has a superficial (drains skin) and a deep system (glans and corporal bodies).

The lymphocapillary networks of the penis originate from the skin, mucous membranes of the urethra (mucosa and sub mucosa), septum of the glans, tunica albuginea of the corpora cavernosum and the fasciae (superficial dartos and deep Bucks').

The lymphatics from the skin of the glans freely communicate and arise radially from the urethral meatus and converge as a single network at the corona. From here they course through the lymphatics of the inner and outer prepucial skin. The skin of the rest of the shaft has rather segregated lymphatic networks that run longitudinally. Similarly the tunica albuginea and fasciae have separate lymphatic channels.

The penile shaft lymphatics converge on the dorsum and ramify to both sides of the groin to drain into the inguinal lymph nodes. **Anatomic crossover occurs in more than 80%.** Few studies have claimed the lymphatics from the flans and the tunica can directly drain into the pelvic lymph nodes – but these have been refuted.

The inguinal lymph nodes may be classified as superficial and deep **with respect to the fascia lata**.

Rouviere (and later Daseler) classified the inguinal nodes five groups – superomedial, superolateral, inferomedial , inferolateral and the central deep nodes.

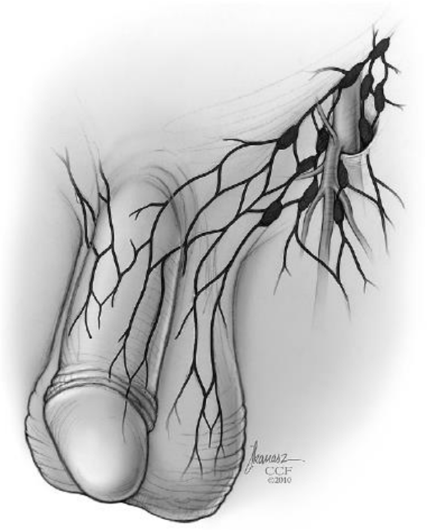


Fig. 2. Penile lymphatic drainage to the inguinal region. (*Courtesy of* Cleveland Clinic Foundation, Inc., Cleveland, OH.)

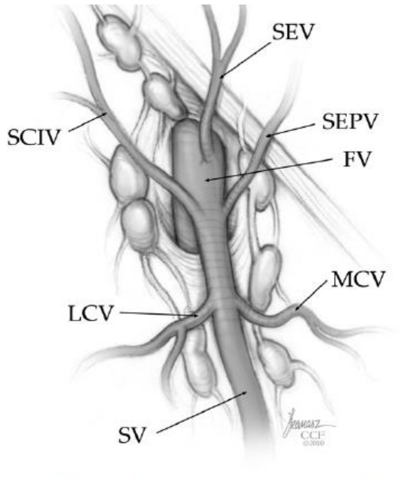


Fig. 3. Major branches of the femoral vein (FV) and their relationship with the surrounding superficial inguinal LNs. LCV, lateral cutaneous vein; MCV, medial cutaneous vein; SCIV, superficial circumflex iliac vein; SEPV, superficial external pudendal vein; SEV, superficial epigastric vein; SV, saphenous vein. (*Courtesy of* Cleveland Clinic Foundation, Inc., Cleveland, OH.)

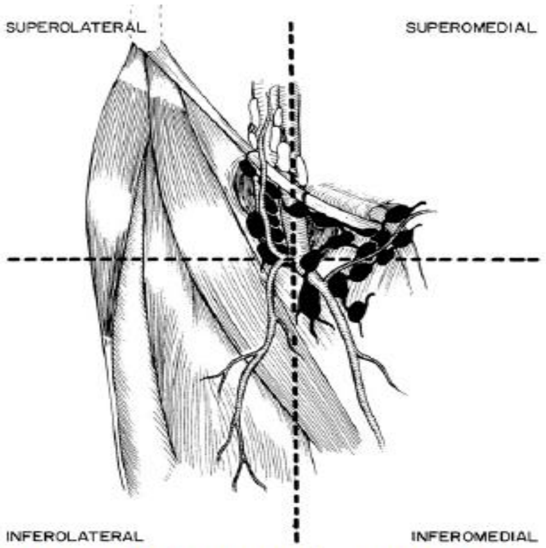


Fig. 4. Superficial inguinal nodes were initially organized by Rouviere into 5 zones (superomedial, superolateral, inferomedial, inferolateral, and central). The central zone is not pictured. (*From* Colberg JW, Andriole GL, Catalona WJ. Penectomy and inguinal lymphadenectomy for carcinoma of the penis. In: Marshall FF, editor. Textbook of operative urology. 1st edition. Philadelphia: WB Saunders; 1996. p. 639, Chapter 76; with permission.)

Most of the lymphatic drainage first occurs to **the superomedial group** (anterior and medial to the superior epigastric vein and superomedial to the junction of the superficial epigastric vein with the femoral vein). This formed the basis for sentinel lymph node biopsy proposed by **Cabanas in 1977**. However owing to variable drainage anatomic sentinel lymph node biopsy (dissecting only the superomedial region) had high false negative rated (upto 25% in some series) – it is thus not recommended for representative biopsy in a non palpable negative groin. (cf: dynamic sentinel lymph node biopsy as opposed to anatomic sentinel lymph node biopsy may be used in a negative groin in experienced centres with high volume experience).

Management of lymph nodes in carcinoma penis:

The presence and extent of metastasis in the inguinal region are the most important prognostic factors for survival in patients with squamous cell carcinoma of the penis. Unlike other genitourinary malignancies the biology of SCC penis exhibits a prolonged locoregional phase before distant dissemination and hence even after inguinal lymph node metastasis, surgery (lymphadenectomy) can be curative.

However owing to the morbidity of the traditional lymphadenectomy especially among patients with clinically negative groins, the contemporary controversial issues include:

a) Selection of patients for lymphadenectomy vs careful observation
b) Types of procedures to correctly stage with minimal morbidity
c) Multimodal therapy to improve survival in bulky LN metastasis

Palpable groin nodes

Data suggest that pathologic criteria associated with long term survival after attempted curative surgical resection of inguinal metastasis (80% 5 year survival) **include minimal nodal disease(up to 2), unilateral involvement, no evidence of extranodal extension (ENE) and absence of pelvic nodal metastasis**. (5 year survival with less than two inguinal lymph nodes is between 73-88%, more than two is 0-54%. Those with pelvic lymph nodes is about 14%)

If the inguinal lymph nodes are **palpable**, treatment with antibiotics is **no longer advocated** as a tool to select patients who should undergo lymphadenectomy (may be useful to sterilize the inguinal region).

Non palpable groin nodes

The likelihood of micrometastasis in clinically negative groins is **25%.**In negative groins, multiple studies reveal an improvement in survival in those undergoing early therapeutic intervention versus delayed (these also showed that if delayed, those who do experience recurrence can rarely be salvaged). Thus in negative groins, especially in light of decreased morbidity with evolving procedures, **early intervention is preferred**.

Primary tumor characteristics predicating occult metastases – pTis, pTa (verrucous carcinoma) and pT1 grade 1 tumors – pT1a according to AJCC classification - together have a risk of occult metastasis of 0-15% and the pT1 grade 2 tumor without LVI and without deep nodular growth pattern has metastasis less than 9%. Hence these groups may be managed with **watchful waiting** (should include patient counselling regarding periodic intense follow up).

All other primary tumors (pT1 grade 3 i.e, pT1b and above) have a high risk of inguinal metastasis (more than 50%) and hence should go a staging procedure.

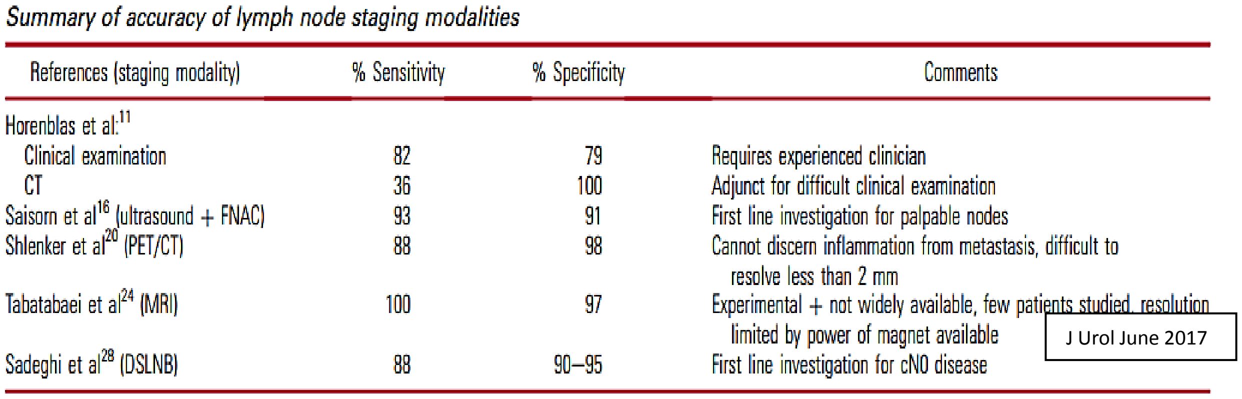
Staging procedures for negative groins:

a) **Dynamic sentinel lymph node biopsy**: has a false negative rate may be as high as 12-15% (varying range). Netherlands group (Sensitivity 98% and specificity 82%).
It is an acceptable option in a high volume centre with standardized protocol.

b) **Superficial lymph node dissection** – Based on frozen section report decision to procede with complete dissection and pelvic lymph node dissection is taken.

c) **Modified complete lymph node dissection** – proposed by Catalona in 1988. Smaller skin incision, lesser area of dissection, thicker skin flaps, preservation of saphenous veins and no Sartorius transposition to decrease morbidity.

d) **Minimally invasive procedures** – robotic and laparoscopic – need further studies to validate use.



Summary of accuracy of lymph node staging modalities

References (staging modality)	% Sensitivity	% Specificity	Comments
Horenblas et al:[11]			
Clinical examination	82	79	Requires experienced clinician
CT	36	100	Adjunct for difficult clinical examination
Saisorn et al[16] (ultrasound + FNAC)	93	91	First line investigation for palpable nodes
Shlenker et al[20] (PET/CT)	88	98	Cannot discern inflammation from metastasis, difficult to resolve less than 2 mm
Tabatabaei et al[24] (MRI)	100	97	Experimental + not widely available, few patients studied, resolution limited by power of magnet available
Sadeghi et al[28] (DSLNB)	88	90–95	First line investigation for cN0 disease

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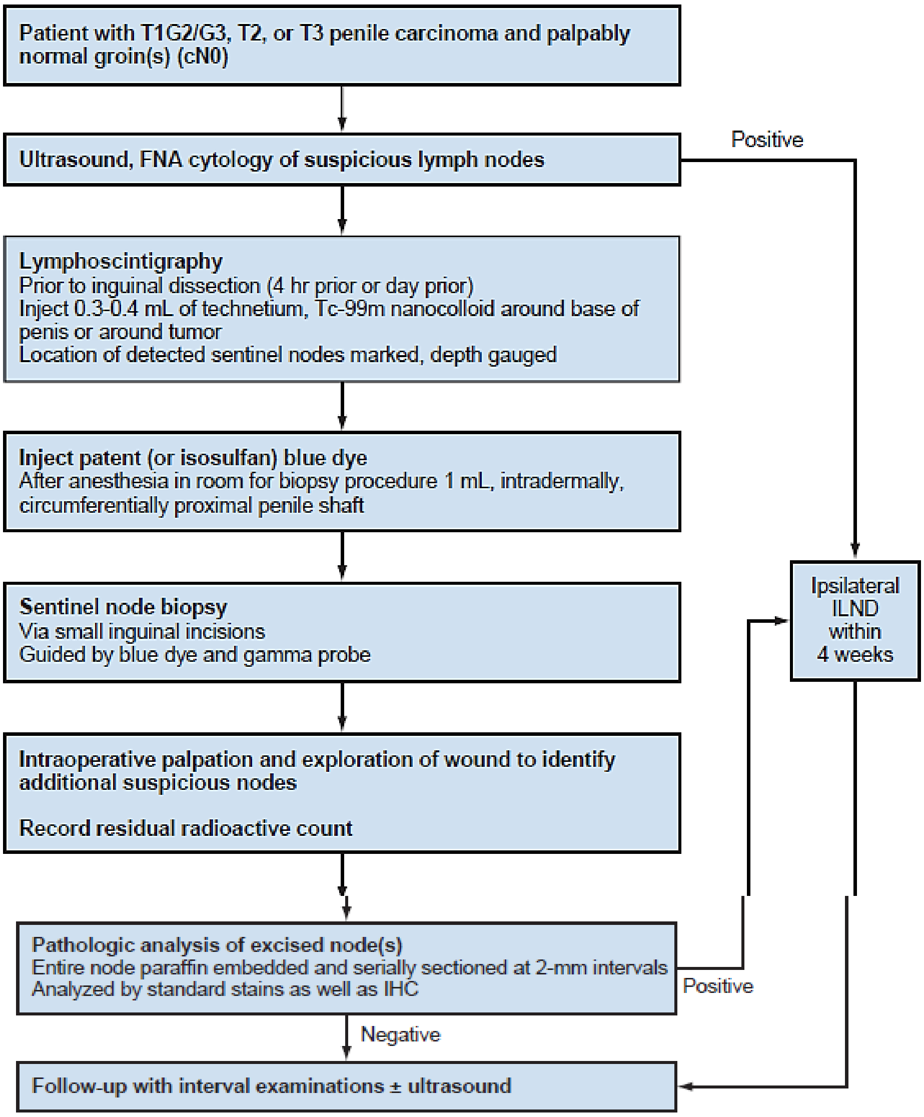

Patient with T1G2/G3, T2, or T3 penile carcinoma and palpably normal groin(s) (cN0)
Ultrasound, FNA cytology of suspicious lymph nodes
Positive
Lymphoscintigraphy
Prior to inguinal dissection (4 hr prior or day prior)
Inject 0.3-0.4 mL of technetium, Tc-99m nanocolloid around base of penis or around tumor
Location of detected sentinel nodes marked, depth gauged
Inject patent (or isosulfan) blue dye
After anesthesia in room for biopsy procedure 1 mL, intradermally, circumferentially proximal penile shaft
Sentinel node biopsy
Via small inguinal incisions
Guided by blue dye and gamma probe
Ipsilateral ILND within 4 weeks
Intraoperative palpation and exploration of wound to identify additional suspicious nodes
Record residual radioactive count
Pathologic analysis of excised node(s)
Entire node paraffin embedded and serially sectioned at 2-mm intervals
Analyzed by standard stains as well as IHC
Positive
Negative
Follow-up with interval examinations ± ultrasound

Figure 39-4. Flow diagram of technique and protocol for dynamic sentinel node biopsy.

BOX 39-1 Criteria for Identifying Suspicious Inguinal Lymph Nodes on Ultrasound

Fine-needle aspiration for cytology is performed if one or more of the following are detected:

- Increased size
- Abnormal shape
    - Rounded, with a short-long axis ratio less than 2
    - Eccentric cortical hypertrophy
- Absence of an echogenic hilum
- Hypoechogenicity of the node compared with adjacent muscle
- Lymph node necrosis
- Abnormal vascularity on power Doppler

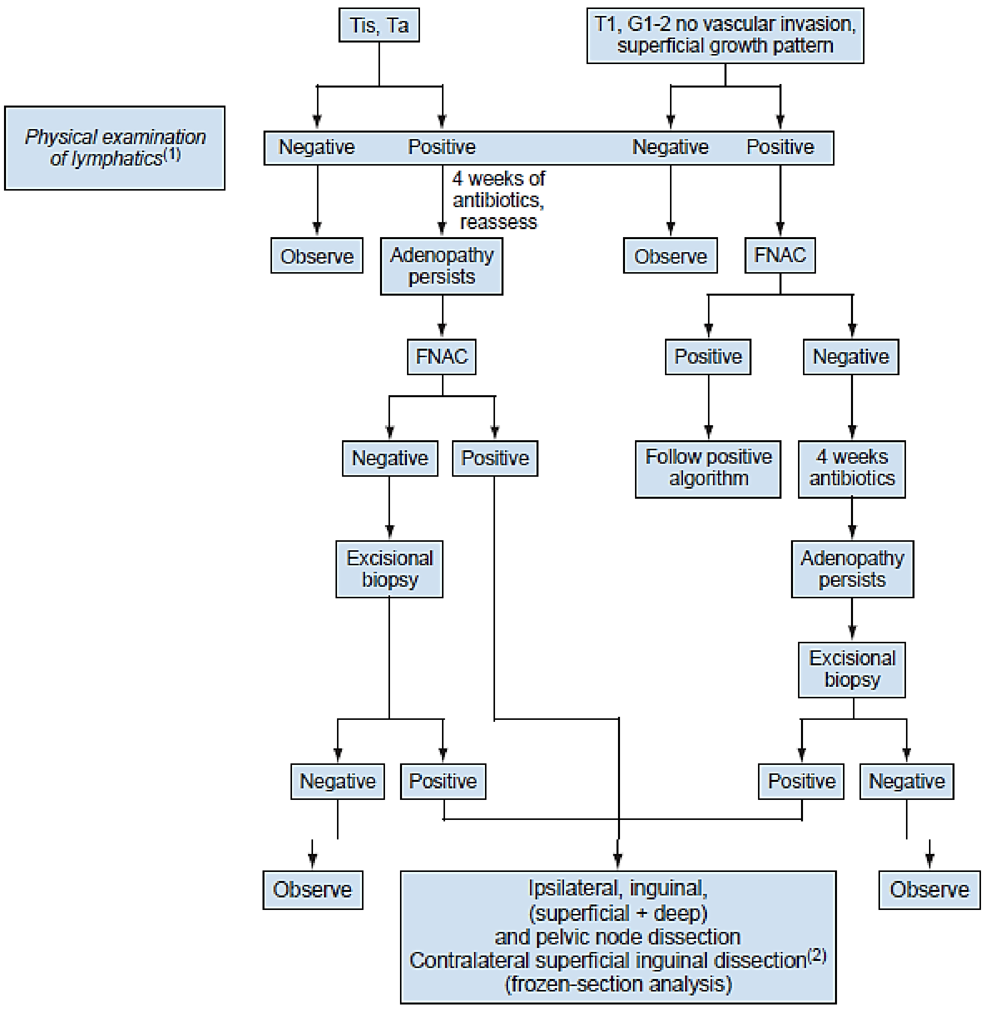
Pelvic lymph nodes:

If 1-3 inguinal lymph nodes are positive, the chance of pelvic LN mets is **22%**. With more than 3 LNs positivity it rises to **57%**.

For patients undergoing inguinal lymph node dissection for curative intent (i.e, preoperative studies reveal no pelvic lymphadenopathy – CT sensitivity for detection of pelvic LNs is only about 38%), pelvic LN dissection should routinely be considered in patients with **two or more positive inguinal LNs or when extranodal extension is present**. Pelvic LN dissection in this setting also serves as an effective staging tool for identifying those at increased risk in whom adjunctive therapy should be considered.

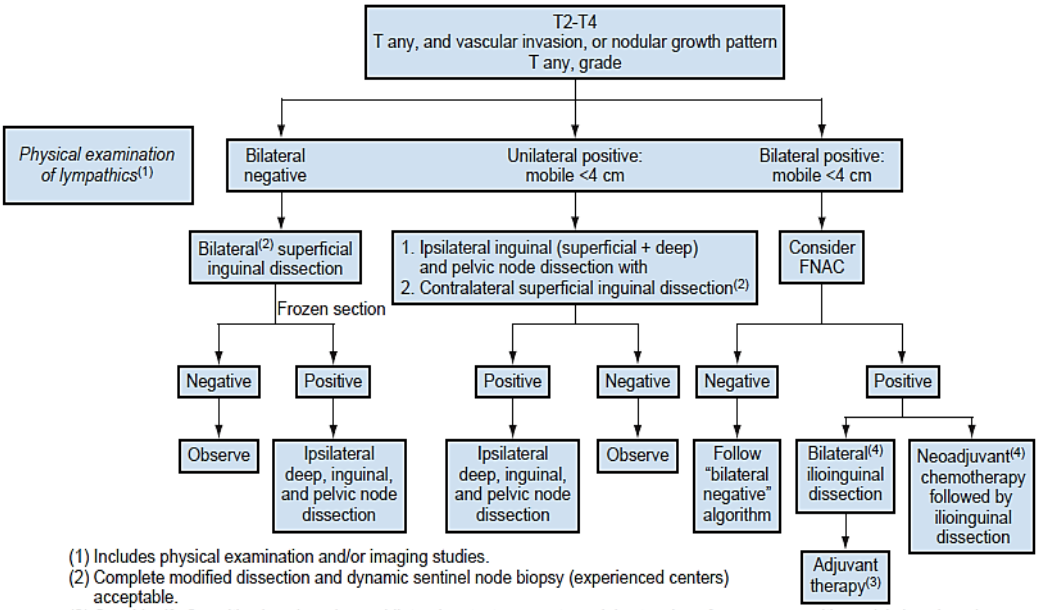
Risk based management of inguinal region:

Low risk group algorithm


Tis, Ta
T1, G1-2 no vascular invasion, superficial growth pattern
Physical examination of lymphatics(1)
Negative
Positive
Negative
Positive
4 weeks of antibiotics, reassess
Observe
Adenopathy persists
Observe
FNAC
FNAC
Positive
Negative
Negative
Positive
Follow positive algorithm
4 weeks antibiotics
Excisional biopsy
Adenopathy persists
Excisional biopsy
Negative
Positive
Positive
Negative
Observe
Ipsilateral, inguinal, (superficial + deep) and pelvic node dissection Contralateral superficial inguinal dissection(2) (frozen-section analysis)
Observe

A (1) Includes physical examination and/or imaging studies.
(2) Complete modified dissection and dynamic sentinel node biopsy (experienced centers) acceptable.

High risk group algorithm


T2-T4
T any, and vascular invasion, or nodular growth pattern
T any, grade
Physical examination of lympathics(1)
Bilateral negative
Unilateral positive: mobile <4 cm
Bilateral positive: mobile <4 cm
Bilateral(2) superficial inguinal dissection
1. Ipsilateral inguinal (superficial + deep) and pelvic node dissection with
2. Contralateral superficial inguinal dissection(2)
Consider FNAC
Frozen section
Negative
Positive
Positive
Negative
Negative
Positive
Observe
Ipsilateral deep, inguinal, and pelvic node dissection
Ipsilateral deep, inguinal, and pelvic node dissection
Observe
Follow "bilateral negative" algorithm
Bilateral(4) ilioinguinal dissection
Neoadjuvant(4) chemotherapy followed by ilioinguinal dissection
Adjuvant therapy(3)

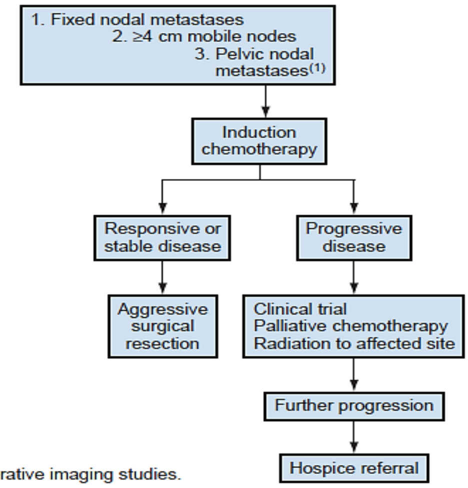
(1) Includes physical examination and/or imaging studies.
(2) Complete modified dissection and dynamic sentinel node biopsy (experienced centers) acceptable.
(3) Consider if >2 positive lymph nodes, or bilateral metastases, extranodal extension of cancer, or positive pelvic lymph nodes.
B (4) Either approach is acceptable.

Management of bulky lymph nodes and fixed metastases

Combination of surgery and chemotherapy has shown some benefit.

Neoadjuvant chemotherapy may be used followed by aggressive surgical resection for those who respond/have stable disease. In progressive disease, palliative groin dissection may be required in conjunction with palliative care.

Patient may be enrolled in clinical trials of novel systemic agents and radiation therapy to affected areas.


1. Fixed nodal metastases
2. ≥4 cm mobile nodes
3. Pelvic nodal metastases(1)
Induction chemotherapy
Responsive or stable disease
Progressive disease
Aggressive surgical resection
Clinical trial
Palliative chemotherapy
Radiation to affected site
Further progression
Hospice referral

C (1) Subsequent to preoperative imaging studies.

Complications of inguinal lymph node surgery include skin flap necrosis, infection, wound dehiscence, seroma and lymphedema. Complications may be reduced by modifies technique or by skin flaps.

Fournier's gangrene

Fournier gangrene is a potentially life-threatening form of necrotizing fasciitis involving the male genitalia. It is also known as idiopathic gangrene of the scrotum, streptococcal scrotal gangrene, perineal phlegmon, and spontaneous fulminant gangrene of the scrotum .

In current practice, in more than 95% the source is identifiable.

Infection most commonly arises from the skin, urethra, or rectal regions.
An association between urethral obstruction associated with strictures and extravasation and instrumentation has been well documented.

Predisposing factors include:

- diabetes mellitus
- local trauma
- paraphimosis
- periurethral extravasation of urine
- perirectal or perianal infections
- surgery such as circumcision or herniorrhaphy

In cases originating in the genitalia, specifically as a result of urethral obstruction, the infecting bacteria probably pass through Buck fascia of the penis and spread along the dartos fascia of the scrotum and penis, Colles fascia of the perineum, and Scarpa fascia of the anterior abdominal wall.

Microorganisms:

In view of the typical foul odor associated with this condition, a major role for anaerobic bacteria is likely.
Wound cultures generally yield multiple organisms, implicating anaerobic-aerobic synergy

Mixed cultures containing facultative organisms *(E. coli*, *Klebsiella,* enterococci) along with anaerobes (*Bacteroides, Fusobacterium, Clostridium,* microaerophilic streptococci) have been obtained from the lesions.

Clinical features:

Patients frequently have a history of recent perineal trauma, instrumentation, urethral stricture associated with sexually transmitted disease, or urethral cutaneous fistula. Pain, rectal bleeding, and a history of anal fissures suggest a rectal source of infection. Dermal sources are suggested by history of acute and chronic infections of the scrotum and spreading recurrent hidradenitis suppurativa or balanitis.

The infection commonly starts as cellulitis adjacent to the portal of entry. Early on, the involved area is swollen, erythematous, and tender as the infection begins to involve the deep fascia. Pain is **prominent, and fever and systemic toxicity are marked**. The swelling and crepitus of the scrotum quickly increase, and dark purple areas develop and progress to extensive gangrene. If the abdominal wall becomes involved in an obese patient with diabetes, the process can spread very rapidly. Specific genitourinary symptoms associated with the condition include dysuria, urethral discharge, and obstructed voiding. Alterations in mental status, tachypnea, tachycardia, and temperature greater than 38.3° C (101° F) or less than 35.6° C (96° F) suggest gram-negative sepsis.

Lab diagnosis and imaging

- Anemia occurs secondary to a decreased functioning erythrocyte mass caused by thrombosis and ecchymosis coupled with decreased production secondary to sepsis.
- Elevated serum creatinine levels, hyponatremia, and hypocalcemia are common.
- Hypocalcemia is believed to be secondary to bacterial lipases that destroy triglycerides and release free fatty acids that chelate calcium in its ionized form.
- Because crepitus is often an early finding, a plain film of the abdomen may be helpful in identifying air. Scrotal ultrasonography is also useful in this regard.
- Biopsy of the base of an ulcer is characterized by superficially intact epidermis, dermal necrosis, and vascular thrombosis and polymorphonuclear leukocyte invasion with subcutaneous tissue necrosis.

Management

Prompt diagnosis is critical because of the rapidity with which the process can progress. The clinical differentiation of necrotizing fasciitis from cellulitis may be difficult because the initial signs including pain, edema, and erythema are not distinctive. However, **the presence of marked systemic toxicity out of proportion to the local finding should alert the clinician**.

Intravenous hydration and antimicrobial therapy are indicated in preparation for surgical debridement. Antimicrobial regimens include broad-spectrum antibiotics (β-lactam plus β-lactamase inhibitor) such as piperacillin-tazobactam, especially if *Pseudomonas* is suspected, ampicillin plus sulbactam, or vancomycin or carbapenems plus clindamycin or metronidazole.

Immediate debridement is essential. In the patient in whom diagnosis is clearly suspected on clinical grounds (deep pain with patchy areas of surface hypoesthesia or crepitation, or bullae and skin necrosis), direct operative intervention is indicated.
Extensive incision should be made through the skin and subcutaneous tissues, going beyond the areas of involvement until normal fascia is found. Necrotic fat and fascia should be excised, and the wound should be left open. A second procedure 24 to 48 hours later is indicated if there is any question about the adequacy of initial debridement.
Orchiectomy is almost never required, because the testes have their own blood supply independent of the compromised fascial and cutaneous circulation to the scrotum.
Suprapubic diversion should be performed in cases in which urethral trauma or extravasation is suspected. **Colostomy** should be performed if there is colonic or rectal perforation.
Hyperbaric oxygen therapy has shown some promise in shortening hospital stays, increasing wound healing, and decreasing the gangrenous spread when used in conjunction with debridement and antimicrobials.

Outcome:

The mortality rate averages approximately **20%**. Higher mortality rates are found in diabetics, alcoholics, and those with colorectal sources of infection who often have a less typical presentation, greater delay in diagnosis, and more widespread extension. Regardless of the presentation, Fournier gangrene is a **true urologic emergency** that demands early recognition, aggressive treatment with antimicrobial agents, and surgical debridement to reduce morbidity and mortality.

Chancroid

Chancroid is caused by the gram-negative bacterium ***H. Ducreyi****.* Infection leads to anogenital ulceration and lymphadenitis with progression to **bubo formation**.

The incubation period is **3 to 10 days**, with the initial presentation of a papule that may progress to form an ulcer. **Painful deep purulent ulcers** (2–20 mm) develop from a papule or pustula. In addition purulent lymphadenopathy develops.

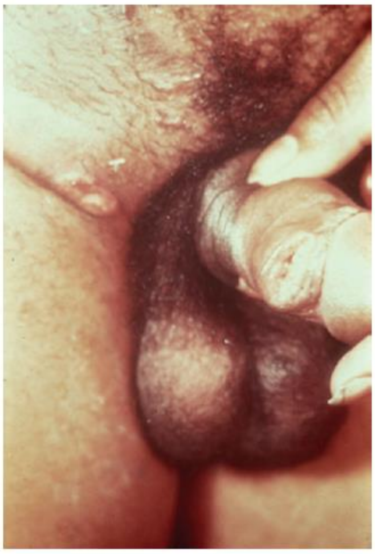


Figure 15-6. Chancroid with regional adenopathy.

Circumcised men are at lower risk of being infected with chancroid.

A genital ulcer in a person with a history of travel to Latin America, Asia or Caribbean should raise suspicion for chancroid.

Chancroid, like genital herpes and syphilis, is **a risk factor for transmission of HIV**.

A definitive diagnosis of chancroid requires culture on media not routinely available.

There are no FDA-approved tests.

The CDC suggests that a probable diagnosis of chancroid can be made if

1. The patient has one or more painful ulcers
2. No evidence of *T. pallidum* is present on darkfield examination of ulcers or by serologic testing for syphilis performed at least 7 days after onset of the ulcers
3. Ulcers and lymphadenopathy,if present, are typical for chancroid
4. Results of tests for HSV on the ulcer exudate are negative

Treatment is with **azithromycin 1 g in a single dose or ceftriaxone 250 mg IM in single dose** or **ciprofloxacin 500 mg orally twice per day for 3 days or erythromycin base 500 mg orally three times per day for 7 days**. Patients should be tested **for HIV** at the time of diagnosis of chancroid. If initial test results were negative, **repeat** testing at 3 months for syphilis and HIV should be performed.

Patients with HIV are less likely to respond to treatment, have slower healing of ulcers, and may require longer courses of therapy.

Table 1. Differential Diagnosis of Genital Ulcers

Infectious (most common)*	Noninfectious (less common)
Genital herpes simplex virus	Behçet syndrome
Syphilis	Fixed drug eruption
Chancroid	Psoriasis
Lymphogranuloma venereum	Sexual trauma
Granuloma inguinale (donovanosis)	Wegener granulomatosis
Fungal infection (e.g., Candida)	
Secondary bacterial infection	

Table 2. Risk Factors for Genital Ulcers

History of inflammatory disease (e.g., psoriasis) and exposure to trauma or medications such as nonsteroidal anti-inflammatory drugs, antimalarials, angiotensin-converting enzyme inhibitors, beta blockers, lithium, salicylates, or corticosteroids

Lack of male circumcision

Multiple sex partners, lifetime or current

Nonrecognition of ulcers in prodrome stage

Serodiscordant sex partners (i.e., one partner with herpes simplex virus and one without)

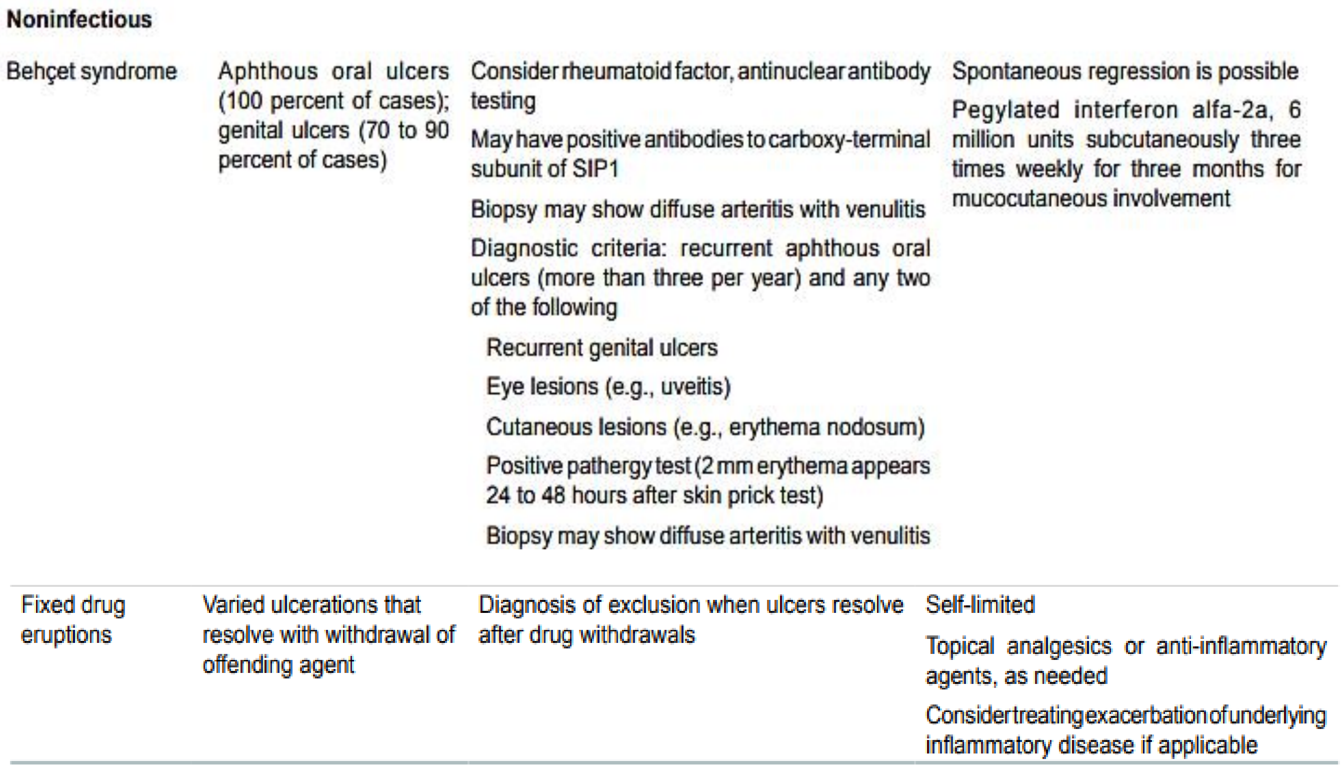
Unprotected sexual contact

Unprotected skin-to-skin contact with ulcers

Table 3. Summary of the Diagnosis and Treatment of Genital Ulcers

Etiology	Clinical presentation	Diagnosis	Treatment options
Infectious*			
Herpes simplex virus infection	Usually multiple vesicular lesions that rupture and become painful, shallow ulcers (Figure 1) Constitutional symptoms, lymphadenopathy in first-time infections	Definitive: herpes simplex virus identified on culture or polymerase chain reaction testing of ulcer scraping or vesicle fluid aspirate Presumptive: typical lesions and any of the following factors Previously known outbreak Positive Tzanck smear of ulcer scraping Exclusion of other causes of ulcers Fourfold increase in acute and convalescent antibody titer results (in a first-time infection)	First episode Acyclovir, 400 mg orally three times daily for seven to 10 days, or 200 mg orally five times daily for seven to 10 days Famciclovir, 250 mg orally three times daily for seven to 10 days Valacyclovir, 1,000 mg orally twice daily for seven to 10 days Recurrent episode Acyclovir, 400 mg orally three times daily for five days, 800 mg orally twice daily for five days, 800 mg orally three times daily for two days, or 200 mg orally five times daily for five days Famciclovir, 1,000 mg twice daily for one day, 500 mg orally once then 250 mg twice daily for two days, or 125 mg orally twice daily for five days Valacyclovir, 500 mg orally twice daily for three days or 1,000 mg orally once daily for five days Suppressive therapy Acyclovir, 400 mg orally twice daily or 200 mg orally three to five times daily Famciclovir, 250 mg orally twice daily Valacyclovir, 1,000 mg orally once daily Valacyclovir, 500 mg orally once daily, if fewer than 10 outbreaks per year

Syphilis (primary)	Single, painless, well-demarcated ulcer (chancre) with a clean base and indurated border (Figure 2) Mild or minimally tender inguinal lymphadenopathy	*Treponema pallidum* identified on darkfield microscopy or direct fluorescent antibody testing of a chancre or lymph node aspirate *or* Positive result on serologic nontreponemal testing (i.e., Venereal Disease Research Laboratories or rapid plasma reagin) that is confirmed with a positive result on serologic treponemal testing (i.e., fluorescent treponemal antibody absorption *or T. pallidum* passive agglutination)	Penicillin G benzathine, 2.4 million units intramuscularly in a single dose
Chancroid	Nonindurated, painful with serpiginous border and friable base; covered with a necrotic, often purulent exudate (Figure 3) Tender, suppurative, unilateral inguinal lymphadenopathy or adenitis	Gram stain suggestive of *Haemophilus ducreyi* (gram-negative, slender rod or coccobacillus in a "school of fish" pattern) Definitive: *H. ducreyi* identified on culture Presumptive: painful genital ulcer or ulcers with regional lymphadenopathy and no evidence of *T. pallidum* infection at least seven days after ulcer onset, and testing negative for herpes simplex virus	Needle aspiration of fluctuant buboes Azithromycin, 1 g orally in a single dose Ceftriaxone, 250 mg intramuscularly in a single dose Ciprofloxacin, 500 mg orally twice daily for three days† Erythromycin, 500 mg orally four times daily for seven days
Lymphogranuloma venereum	Small, shallow, painless, genital or rectal papule or ulcer; no induration Unilateral, tender inguinal or femoral lymphadenopathy Rectal bleeding, pain, or discharge; ulcerative proctitis; constipation or tenesmus	Definitive: *Chlamydia trachomatis* serotype L1, L2, or L3 culture, identified from clinical specimen *or* Immunofluorescence demonstrating inclusion bodies in leukocytes of an inguinal lymph node (bubo) aspirate *or* Microimmunofluorescence positive for lymphogranuloma venereum strain of *C. trachomatis* Presumptive: Clinical suspicion Community prevalence Exclusion of other causes of proctocolitis, inguinal lymphadenopathy, or genital ulcers	Doxycycline, 100 mg orally twice daily for 21 days Erythromycin base, 500 mg orally four times daily for 21 days Pregnant or lactating women: erythromycin, 500 mg orally four times daily for 21 days
Granuloma inguinale (donovanosis)	Persistent, painless, beefy-red (highly vascular) papules or ulcers (Figure 4) May be hypertrophic, necrotic, or sclerotic No lymphadenopathy May have subcutaneous granulomas	Definitive: Intracytoplasmic Donovan bodies on Wright stain *or* Positive result with Giemsa stain or biopsy of granulation tissue	Treatment should continue until lesions have healed Doxycycline, 100 mg orally twice daily for at least 21 days Azithromycin, 1 g orally once weekly for at least 21 days Ciprofloxacin, 750 mg orally twice daily for at least 21 days Erythromycin base, 500 mg orally four times daily for 21 days Trimethoprim/sulfamethoxazole double strength, 160/800 mg orally twice daily for at least 21 days



Noninfectious			
Behçet syndrome	Aphthous oral ulcers (100 percent of cases); genital ulcers (70 to 90 percent of cases)	Consider rheumatoid factor, antinuclear antibody testing May have positive antibodies to carboxy-terminal subunit of SIP1 Biopsy may show diffuse arteritis with venulitis Diagnostic criteria: recurrent aphthous oral ulcers (more than three per year) and any two of the following Recurrent genital ulcers Eye lesions (e.g., uveitis) Cutaneous lesions (e.g., erythema nodosum) Positive pathergy test (2 mm erythema appears 24 to 48 hours after skin prick test) Biopsy may show diffuse arteritis with venulitis	Spontaneous regression is possible Pegylated interferon alfa-2a, 6 million units subcutaneously three times weekly for three months for mucocutaneous involvement
Fixed drug eruptions	Varied ulcerations that resolve with withdrawal of offending agent	Diagnosis of exclusion when ulcers resolve after drug withdrawals	Self-limited Topical analgesics or anti-inflammatory agents, as needed Consider treating exacerbation of underlying inflammatory disease if applicable

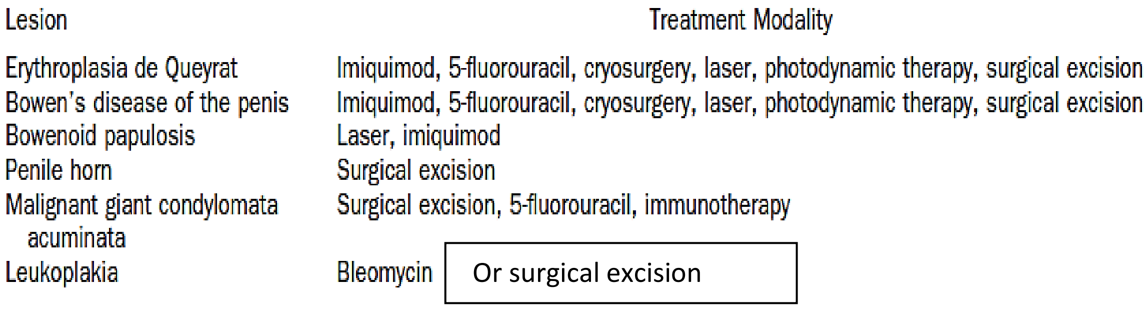
Penile premalignant lesions/Penile intraepithelial neoplasia (PIN)

Non-HPV related:

a) Cutaneous horn – overgrowth and cornification of pre-existing skin lesions. May be associated with HPV 16. Surgical excision is the treatment.
b) Pseudoepitheliomatous micaceous keratitis balanitis (PEKM) – Microscopically mimics verrucous carcinoma.
c) BXO
d) Leukoplakia – common in diabetics – associated with CIS and verrucous carcinoma. Solitary of multiple whitish plaques often involves meatus.
e) Paget's disease – slow growing intraepithelial adenocarcinoma. May be associated with other visceral malignancies including other genitourinary malignancies.

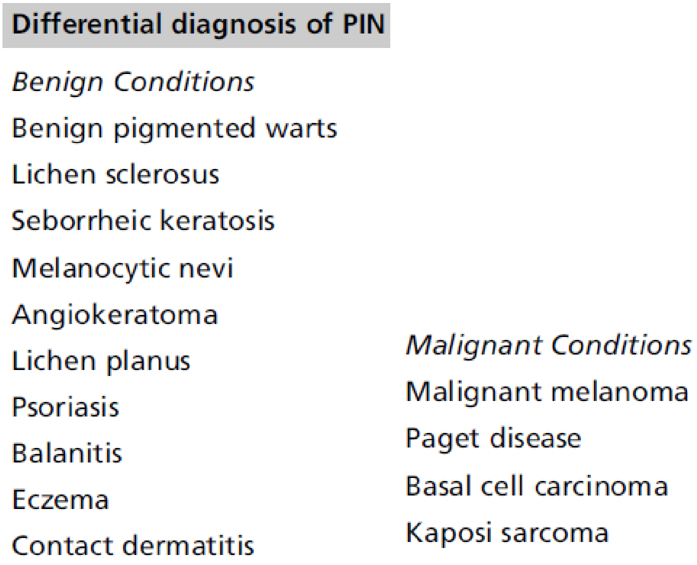
HPV related:

a) Condyloma acuminatum (Giant condymloma=Bushke Lowenstein= verrucous carcinoma=locally invades, no metastatic potential) – Excision is the treatment of choice. RT is to be avoided due to potential malignant degeneration.
b) Bowenoid papulosis
c) Bowens disease (CIS of follicle bearing skin of genitalia)
d) Erythroplasia of Querat (CIS of glans and prepuce)



Lesion	Treatment Modality
Erythroplasia de Queyrat	Imiquimod, 5-fluorouracil, cryosurgery, laser, photodynamic therapy, surgical excision
Bowen's disease of the penis	Imiquimod, 5-fluorouracil, cryosurgery, laser, photodynamic therapy, surgical excision
Bowenoid papulosis	Laser, imiquimod
Penile horn	Surgical excision
Malignant giant condylomata acuminata	Surgical excision, 5-fluorouracil, immunotherapy
Leukoplakia	Bleomycin Or surgical excision

Penile intraepithelial neoplasia (PIN)



Differential diagnosis of PIN

Benign Conditions

Benign pigmented warts
Lichen sclerosus
Seborrheic keratosis
Melanocytic nevi
Angiokeratoma
Lichen planus
Psoriasis
Balanitis
Eczema
Contact dermatitis

Malignant Conditions

Malignant melanoma
Paget disease
Basal cell carcinoma
Kaposi sarcoma

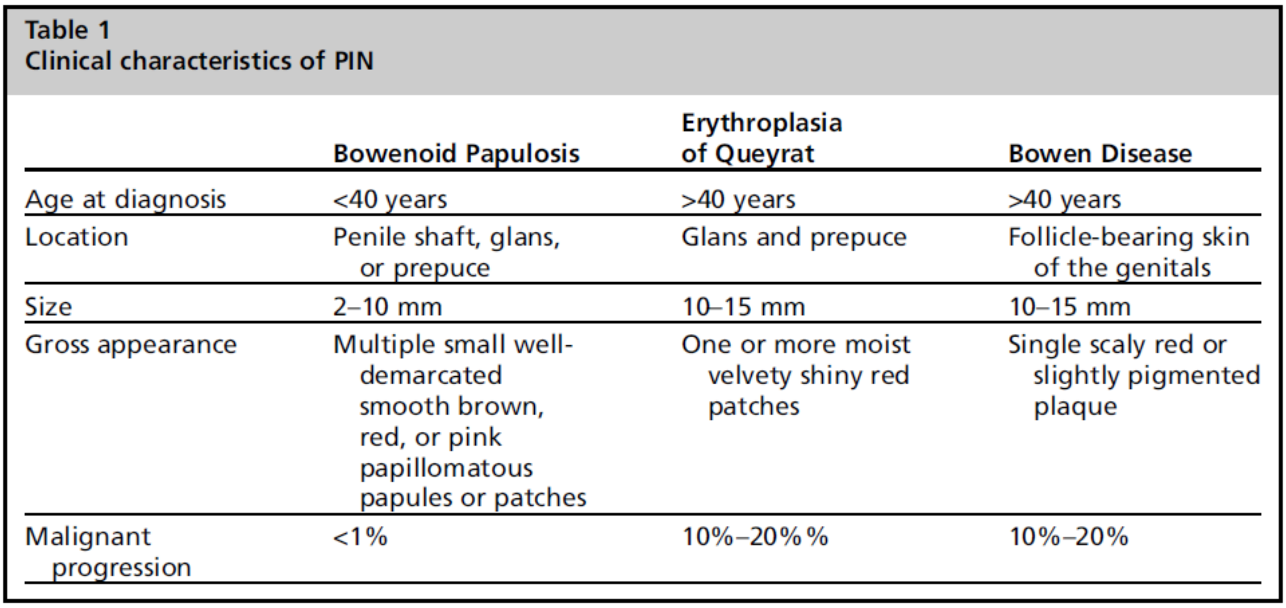


Table 1
Clinical characteristics of PIN

	Bowenoid Papulosis	Erythroplasia of Queyrat	Bowen Disease
Age at diagnosis	<40 years	>40 years	>40 years
Location	Penile shaft, glans, or prepuce	Glans and prepuce	Follicle-bearing skin of the genitals
Size	2–10 mm	10–15 mm	10–15 mm
Gross appearance	Multiple small well-demarcated smooth brown, red, or pink papillomatous papules or patches	One or more moist velvety shiny red patches	Single scaly red or slightly pigmented plaque
Malignant progression	<1%	10%–20%%	10%–20%

Treatment options for CIS:

1) Topical chemotherapy – 5-Fluorouracil/Imiquimod may be used as first line treatment. Complete response rate is around 57%. Long term follow up is required to pick local recurrence.
2) LASER – Nd:YAG or CO2 LASER ablation with/without photodynamic control for better tumor detection.
3) Radiotherapy – For lesions less than 4 cm EBRT with boost/brachytherapy may be used. RT should not be used for verrucous carcinoma (treatment for verrucous carcinoma is excision).
4) Total/partial glans resurfacing – May have invasive component up to 20%. Introp frozen section is needed to confirm negative margins.
5) For failed organ preserving procedures/for recurrences partial penectomy may be done.

Organ preserving treatment for penile cancer

A penis-preserving strategy is recommended for **small and localised invasive lesions (Ta/T1a)**. It is **mandatory to do a biopsy to confirm diagnosis prior** to using conservative treatments. All patients must be **circumcised before** considering conservative non-surgical treatments (For better local focal action, lesser local toxicity and surveillance).

For tumours confined to the prepuce**, radical circumcision** alone may be curative provided that negative surgical margins are confirmed by definitive histology.

For all surgical treatment options, the intra**-operative assessment of surgical margins by frozen section** is recommended as tumour-positive margins lead to local recurrence.
Total removal of the glans (glansectomy) and prepuce has the lowest recurrence rate for the treatment of small penile lesions (2%).
Negative surgical margins are imperative when using penile-conserving treatments and **a margin of 5 mm is considered oncologically safe**.
Treatment choice depends on tumour size, histology, including stage and grade, localisation (**especially relative to the meatus**) and patient preference as there **are no documented differences** in long-term local recurrence rates between surgery, laser and radiation therapy.

The various organ preserving options are:

1) **Circumcision alone** – For tumors confined to the prepuce alone
2) **Laser therapy** – With Nd:YAG or CO2. Visualisation may be improved by photodynamic diagnosis. The depth of penetration of CO2 Laser is only 0.1mm while protein denaturation with Nd:YAG occurs upto 6mm.
   For T1 tumors local recurrence using CO2 Laser ranges from 14-23% while inguinal nodal recurrence was 0-4%. Nd:YAG laser local recurrence ranges from 10-48% with inguinal nodal recurrence of 21%. Other Lasers used include KTP Laser.
3) **Mohs' micrographc surgery** - Moh's micrographic surgery is a technique by which histological margins are taken in a geometrical fashion around conus of excision. This technique has not been widely used. In Moh's series, 79% were cured at five years.
4) **Simple excision and primary closure** – For small tumors this may be used.

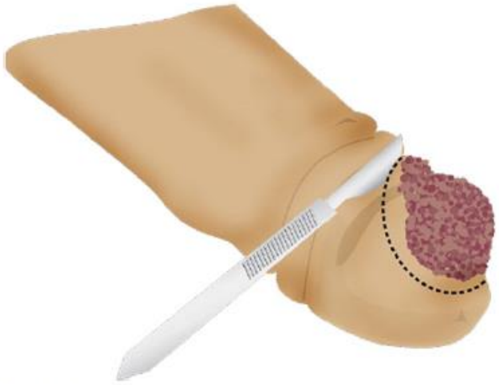
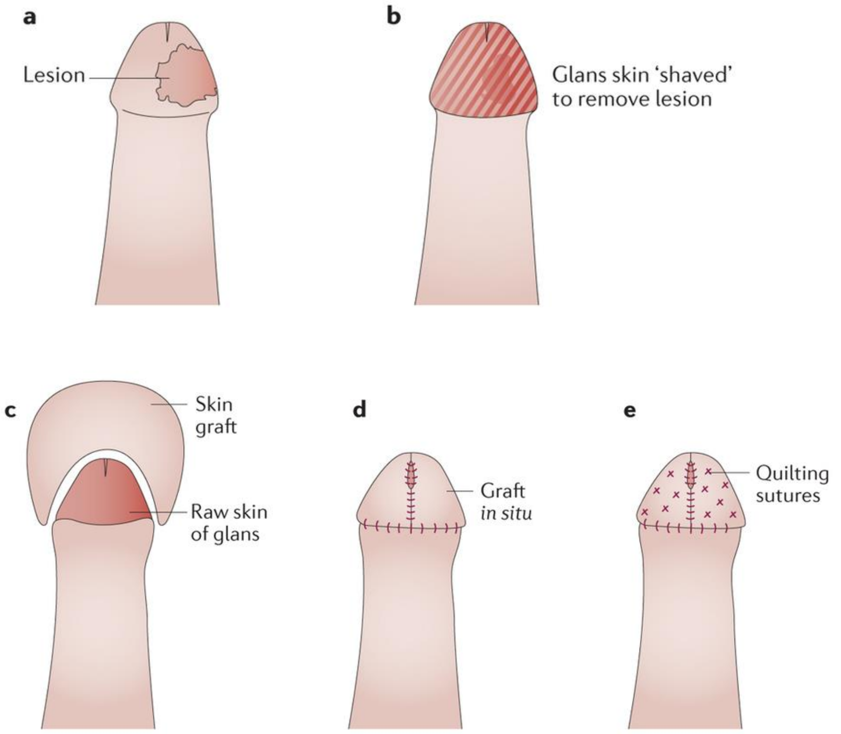


Fig. 2. Simple closure.

5) **Glans resurfacing** – The local recurrence was between 0-6 percent.



a | A penile lesion involving a large proportion of the glans is suitable for glans resurfacing. **b** | 'Shaving' of the lesion off the glans removes the tumour. **c** | An extragenital skin graft is prepared and applied over the raw skin of the glans. **d** | the skin graft is stitched to cover the glans and create a neomeatus, with approximation of the shaft skin. **e** | Quilting of the neoglans is carried out to promote 'graft take'.

6) **Glansectomy** – A total glansectomy removes the entire glans leaving no residual glandular tissue that may be source for recurrence. Defect can be closed with prepucial skin flap or STSG. Local recurrence rates of 8-12% and node recurrence rates of 2-9%.

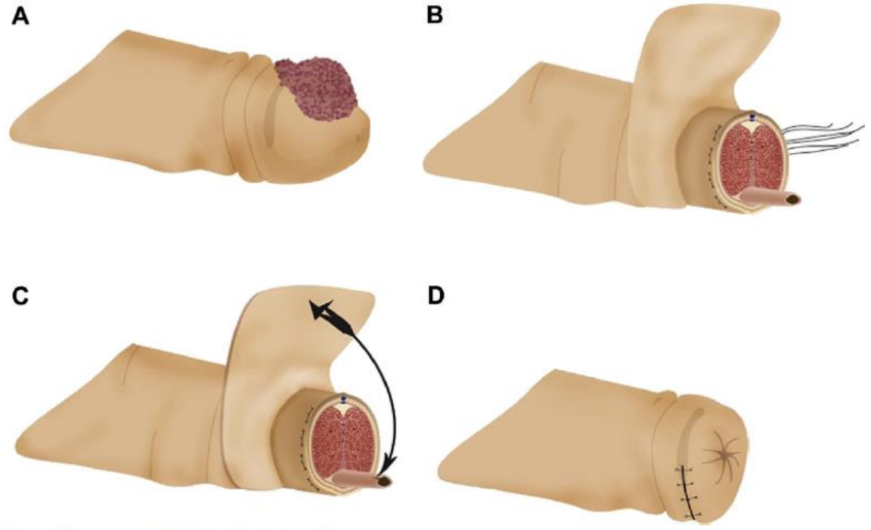


Fig. 3. Glansectomy with preputial flap closure.

7) **Partial penectomy** - The local recurrence rates in various heterogeneous studies range from 4-50%. 5 year survival rate range from 59-90%

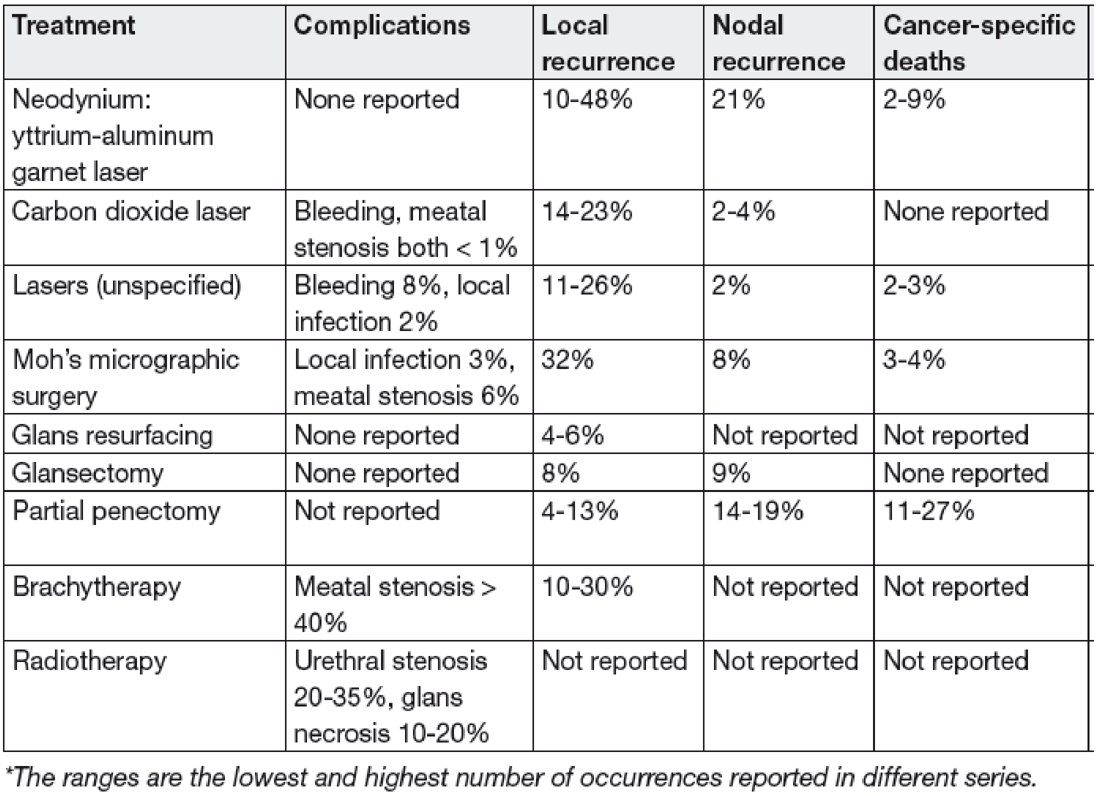
8) Radiation treatment for T1 and T2 disease – may be used for T1 and T2 disease as an alterantive organ preserving treatment. The diameter of the lesion should be **less than 4 cm.**

EBRT 60Gy combined with boost or brachytherapy alone is used. Local disease free rates range from 70-90%. Patients with >4cm lesion are not candidates for RT.

Common complications with RT include urethral stenosis (20-35%), glans necrosis (10-20%), meatal stenosis (especially with brachytherapy - >40%) and late fibrosis of corpora cavernosa.

All penile preserving strategies have good quality of life and better sexual function than radical surgery. (Better cosmetic and functional outcomes)

Summary of local treatment



Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths
Neodynium: yttrium-aluminum garnet laser	None reported	10-48%	21%	2-9%
Carbon dioxide laser	Bleeding, meatal stenosis both < 1%	14-23%	2-4%	None reported
Lasers (unspecified)	Bleeding 8%, local infection 2%	11-26%	2%	2-3%
Moh's micrographic surgery	Local infection 3%, meatal stenosis 6%	32%	8%	3-4%
Glans resurfacing	None reported	4-6%	Not reported	Not reported
Glansectomy	None reported	8%	9%	None reported
Partial penectomy	Not reported	4-13%	14-19%	11-27%
Brachytherapy	Meatal stenosis > 40%	10-30%	Not reported	Not reported
Radiotherapy	Urethral stenosis 20-35%, glans necrosis 10-20%	Not reported	Not reported	Not reported

**The ranges are the lowest and highest number of occurrences reported in different series.*

Verrocous carcinoma

Verrucous carcinoma is a **locally aggressive, exophytic, low-grade variant of SCC** that has little metastatic potential.

The **Buschke-Lowenstein tumor is a verrucous carcinoma of the anogenital mucosal surface** and may represent up to 24% of all penile tumours.

It most commonly occurs in uncircumcised men on the glans or prepuce, although similar lesions can be found on the vulva, vagina cervix, or anus.

Verrucous carcinoma has been associated **with HPV type 6 and 11** infection but not with the more classically oncogenic types 16 and 18.

- Verrucous carcinoma lesions have a warty appearance and are often large and fungating when presenting on the genitalia. Aside from genital sites, these lesions can also present within the oral and nasal cavities and plantar surfaces of the feet.

- They are **slowly growing and locally destructive**, often extending deeply into underlying tissue.

- Preferred treatment is by **local excision**.
- Mohs micrographic surgery may be helpful in tracing out the tumor and minimizing tissue loss.

- **Primary radiotherapy is relatively contraindicated because of the potential for anaplastic transformation** with a subsequent increase in metastatic potential**.**

Varicocele in male infertility

Varicocele is the **most common non-ductal surgically correctable cause of male infertility**.

Varicocelectomy is the **most commonly performed operation for treatment of male infertility**.

Varicocele is found in approximately **15% of general population**, **35% of men with primary infertility** and **75-81% of men with secondary infertility**.

Varicocele is associated **with progressive and duration dependent** decline in testicular function (spermatogenesis and Leydig cell function).

Varicoceles arise because of intravenous valvulur incompetence. Genetics may predispose to vavlular defect as studies have shown there is increased incidence in first degree relatives affected.

Around **80-90%** varicoceles are **left sided** because (abrupt onset right varicocele suspect right renal/retroperitoneal pathology):

a) Left testicular vein joins at right angles to left renal vein
b) Left testicular vein joins renal vein 8-10 cm cranial to the right testicular vein joining IVC. This leads to added hydrostatic pressure.(i.e, left testicular vein longer)
c) Loaded sigmoid colon
d) Left testicular artery arches over vein.
e) Incompetent valves more common
f) Left renal vein may be compressed between SMA and aorta (nutcracker)

Mechanism of varicocele exerting deleterious effect on male reproductive function:

1) Increases intratesticular temperature due to interruption in counter-current heat exchange between pampiniform plexus and testicular artery. This may lead to oxidative stress, metabolic and ion changes, DNA fragmentation and aneuploidy.
2) Reflux of renal and adrenal metabolites.
3) Impaired venous drainage –accumulation of gonadotoxins, oxidative stress and hypoxia.
4) Increased hydrostatic pressure.

Clinical features:

Presentation is with swelling; dull dragging scrotal pain or infertility. Physical examination should include examination of the patient for dilated veins in standing position and measurement of testicular size with orchidometer.

Clinical grading for varicocele:

1) Grade 1: Not palpable or visible – only detected on Doppler USG.
2) Grade 2: Palpable (may be with Valsalva) but not visible.
3) Grade 3: So large that is visible.

Objective measurement of testicular size may be done with orchidometers (Prader, Seagars' or skinfold callipers) or using ultrasonography. Ultrasonography has a high degree of accuracy and reproducibility and hence is the standard for testicular volume measurement. (cf: **USG is not used as a diagnostic tool to rely on for varicocele identification** because it is not likely to affect treatment outcome. Varicoceles become palpable at about 2.7mm-3.5mm diameter, those smaller than these that are detected on USG i.e, subclinical varicoceles do not benefit from treatment)

Semen analysis is done in:

a) Couple with infertility attempting to conceive has a varicocele (Female factor ruled out).
b) An adult male not currently attempting to achieve conception, but has a palpable varicocele and a desires for future fertility.
c) Young adult males with varicoceles at risk for progressive testicular dysfunction.

Indications for treatment:

1) Varicocele is palpable on physical examination with:
    a) The couple has known infertility
    b) Female partner has normal fertility or a potentially treatable cause of infertility
    c) Male partner has abnormal semen parameters
2) Palpable varicocele and abnormal semen analyses, not currently attempting to conceive
3) Varicocele and objective evidence of reduced ipsilateral testicular size (20% difference in size)
4) Other indications :
    a. Pain related to varicocele.
    b. Decreased testosterone level with large varicoceles.

(There is an old question on adolescent varicocele; the only change would be the indications for surgery:

1) Persisitent testis volume differential >20% in children too young to be evaluated with semen analysis
2) Low total testis volume in a Tanner 5 adoloscent (Total volume <30ml) in late adolescence
3) An abnormal semen analysis if a sample can be produced. **)**

Surgical options (Types of varicocelectomy):

Scrotal approach with high chance of testicular artery injury and recurrence is no longer preferred

1) Retroperitoneal approach (Palomo's technique)
2) Laparoscopic varicocelectomy
3) Concentional inguinal approach
4) Microscopic inguinal/sub-inguinal approach
5) Radiographic technique

Retroperitoneal surgery:

- ➢ Incision at level of internal ring
- ➢ At this level only one or two large veins are present
- ➢ High incidence of recurrence when testicular artery is intentionally preserved (periarterial plexus of veins, the venae comitantes establish collaterals and are the commonest cause for recurrence)
- ➢ Less commonly failure is due to parallel retroperitonel collaterals/dilated cremasteric or scrotal collaterals
- ➢ Recurrence can be markedly reduced in children and adolescents by intentional ligation of testicular artery (but effect on spermatogenesis is uncertain)

Laparoscopic varicocelectomy:

- ➢ Similar cons as retroperitoneal approach
- ➢ Magnification provided by laparoscopy allows visualisation of testicular artery and lymphatics better.
- ➢ Serious potential complications include injury to bowel, viscera and vessels and risks of general anaesthesia.
- ➢ Reasonable alterantive in hands of experienced laparoscopist.

Radiographic occlusion:

- ➢ Coil occlusion has success rate of 75-90%
- ➢ Longer procedure (1-3 hours)
- ➢ Recurrence in longer run may be due to recanalization

Conventional inguinal:

- High chance of hydrocele (3-30%)
- Recurrence due to missed veins (no magnification of microsurgical methods)

Microsurgical varicocelectomy (Inguinal/subinguinal):

- Preferred technique
- Advantage of spermatic cord structures pulled out of the wound and microscopy magnification assisted identification of the veins, artery and lymphatics
- Access to external spermatic vein and gubernacular vein if needed
- Access to testis biopsy or examination of epididymis are added benefits
- Introp microdoppler may help identifying artery, in approximately 50% cases artery is adherent to the undersurface of the large vein

The differences, pros and cons of inguinal vs subinguinal are summarized in the table below:

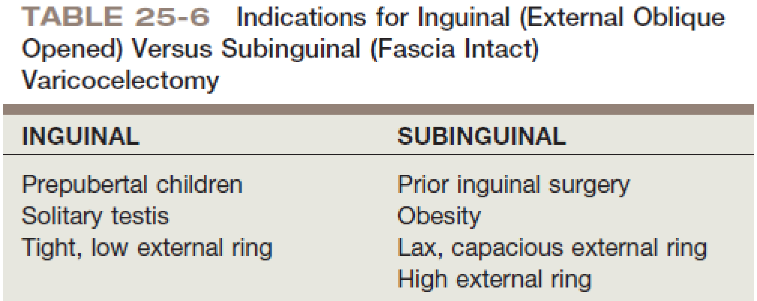


TABLE 25-6 Indications for Inguinal (External Oblique Opened) Versus Subinguinal (Fascia Intact) Varicocelectomy

INGUINAL	SUBINGUINAL
Prepubertal children	Prior inguinal surgery
Solitary testis	Obesity
Tight, low external ring	Lax, capacious external ring
	High external ring
Short cord, high-lying testis	Long cord with low-lying testis
Less experienced with microsurgical repair	Very experienced with microsurgical repair

Simultaneous inguinal hernia repair

Prior failed subinguinal approach

Summary of techniques of varicocelectomy:

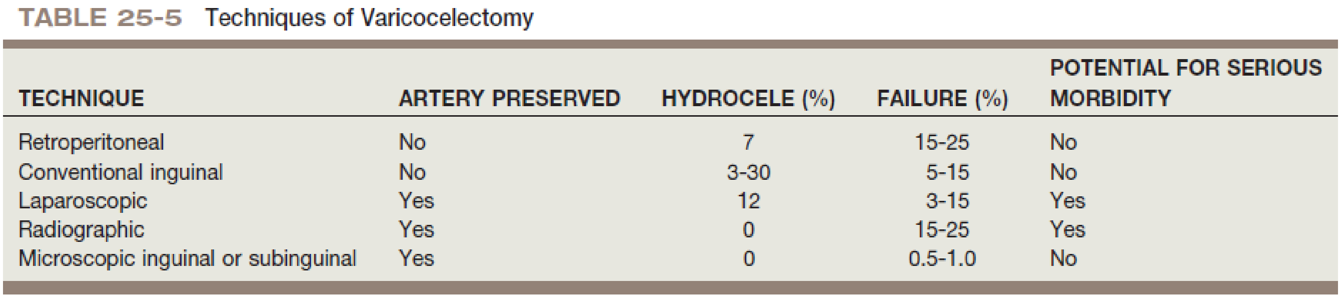


TABLE 25-5 Techniques of Varicocelectomy

TECHNIQUE	ARTERY PRESERVED	HYDROCELE (%)	FAILURE (%)	POTENTIAL FOR SERIOUS MORBIDITY
Retroperitoneal	No	7	15-25	No
Conventional inguinal	No	3-30	5-15	No
Laparoscopic	Yes	12	3-15	Yes
Radiographic	Yes	0	15-25	Yes
Microscopic inguinal or subinguinal	Yes	0	0.5-1.0	No

Complications of varicocelectomy:

1) Hydrocele – due to lymphatic occlusion
2) Testicular artery injury
3) Varicocele recurrence

Results and outcomes:

- **60-80%** have significant improvement in semen parameters
- Pregnancy rates : **20-60%**
- Microsurgical varicocelectomy results in **return of sperm** to the ejaculate in **up to 50% of azoospermic men** with palpable varicoceles.
- Repair of **larger varicoceles results in significantly greater improvement** in semen quality.
- In infertile men with low testosterone, microsurgical varicocelectomy alone results in **substantial improvement in serum testosterone levels.**

Testes

1. Growing teratoma syndrome (GTS)

- **Definition**
  - GTS is defined in the setting of history of NSGCT when there occurs a rapid increase in size of metastatic lesions during or after adequate and appropriately administered systemic chemotherapy, with normal serum tumor markers.
  - GTS is not considered if serum tumor markers are raised.
  - Presence of teratomatous elements in the orchiectomy specimen highly suspicious for GTS
- Incidence: 2.2% (1.9-7.6%)
- Mostly seen in retroperitoneum, but also described in
  - Lung & mediastinum
  - Supraclavicular & inguinal lymph nodes
  - Mesentery, liver & forearm

- **Etiopathogenesis:** Unclear, but the three most-quoted theories are as follows
  - i. Preferential destruction of immature malignant cells by chemotherapy, sparing the mature benign teratomatous elements
  - ii. Alteration of cell kinetics by chemotherapy resulting in transformation of totipotent malignant germ cell into a benign mature teratoma
  - iii. Inherent “Spontaneous differentiation” of malignant cells into benign tissues
- **Clinical features**
  - Reported early during the chemotherapy to as late as 12 years post chemotherapy. GTS may also develop after PC-RPLND
  - Clinical behaviour of GTS is unpredictable for aggressive local spread. It tends to engulf and compress the nearby important structures.
  - Usual presentation is asymptomatic large abdominal mass. Patient may also present with symptoms f compression of important structures e.g. large blood vessels, retroperitoneal nerves resulting in lower limb edema, abdominal pain. Sudden pain can occur due to hemorrhage in the mass. Flank pain is the result of compression of ureter causing HUN.
  - There are no specific criteria for rate of growth. Reported median increase in diameter is 0.7 cm/month (12.9 ml/month).
- **Diagnosis**
  - Patient is labelled to have GTS based on defining criteria. Confirmation of diagnosis is done by the presence of mature teratoma and absence of malignant germ cells on final HPE of surgical resection specimen of mass.

- **Treatment**
  - Chemotherapy & radiation therapy- Not effective
  - Total resection is curative. Surgical approaches described for GTS include:
    - Resection of mass only
    - Template-type dissection
    - Full, bilateral template RPLND (nerve sparing if possible)- preferred in most patients
    - Complete resection of the mass should be the goal whenever possible, because of→
      - High rate of recurrence
        - 0-4% after complete resections
        - 72-83% after partial resections
      - Rare chance of residual malignant component in the post-chemotherapy setting
      - Potential malignant degeneration
  - 5-year overall survival following complete surgery is 90%
  - Mortality mainly related to post-operative complications

- **Good treatment outcomes depends on**
  - Awareness of this condition
  - Vigilant imaging on chemotherapy for NSGCTs. Axial imaging after 2 cycles recommended
  - Early recognition of paradoxical response to chemotherapy (enlarging tumors and normal tumor markers)
  - Early diagnosis
  - Prompt and complete surgical resection of tumors

2. ITGCN

- ITGCN is a histological diagnosis, and **is also referred to as carcinoma in situ (CIS of testis)**. It is diagnosed by testicular biopsy performed for the investigation of infertility, by biopsy of the contralateral testis in a patient with GCT, or by biopsy within the affected testis in a patient undergoing testis-sparing surgery.
- ITGCN appears to develop from arrested primordial germ cells or gonocytes that failed to differentiate into pre-spermatogonia.
  These cells are thought to lie dormant until after puberty when they are stimulated by increased testosterone levels.
- ITGCN consists of undifferentiated germ cells that have the appearance of seminoma that are located basally within
  the seminiferous tubules. The tubule usually shows decreased or absent spermatogenesis, and normal constituents are replaced by ITGCN. ITGCN is much less frequent in pediatric GCTs.
- ITGCN is the precursor lesion for most of GCTs. With the exception of spermatocytic seminoma, all adult invasive GCTs arise from ITGCN.
- **Risk factors for development of ITGCN**
  - History of testicular carcinoma (5% to 6%).
  - EGCT (40%).
  - Cryptorchidism (3%).
  - Contralateral testis with unilateral testicular cancer (5% to 6%).
  - Alrophic contralateral testis with unilateral testicular cancer (30%).
  - Somatosexual ambiguity (25% to 100%).
  - Infertility (0.4% to 1.1%)
- **Clinical significance**
  - Presence of ITGCN in an orchiectomy specimen in men with testicular cancer does not carry any prognostic implications with regard to the risk of relapse of the cancer. However, 5%-9% of patients with GCT have ITGCN within the unaffected contralateral testis. This incidence of contralateral ITGCN increases to about 36% in men with age <40 years, and testicular atrophy or cryptorchidism of contralateral testis. Thus an open inguinal biopsy of the contralateral testis may be considered in patients with risk factors for ITGCN or those with suspicious lesions on preoperative USG.
  - ITGCN in otherwise normal testis carries a high risk of developing invasive GCT.
  - In men with a history of GCT the finding of testicular microlithiasis on ultrasound evaluation of the contralateral testis is associated with an increased risk of ITGCN.
  - When testis-sparing surgery is performed for GCT, biopsies of the adjacent testicular parenchyma should be done to rule out the presence of ITGCN, because ITGCN is present in adjacent testicular parenchyma in 80% to 90% cases of GCT and is associated with a 50% risk of GCT within 5 years and 70% within 7 years.
- **Treatment**
  - Treatment options include orchiectomy, low-dose radiotherapy, and close observation.
  - The choice of therapy should be individualized based on the patient's desire for future paternity, the presence or absence of a normal contralateral testis, and the patient's desire to avoid testosterone replacement therapy.

  1) **Radical orchiectomy**
     - It is the most definitive treatment.
     - It is the preferred option for patients with a normal contralateral testis who desire future paternity, because radiotherapy may impair spermatogenesis in the contralateral testis.
  2) **Low-dose radiotherapy (20 Gy)**
     - RT is associated with similar rates of local control as with orchiectomy with preservation of testicular endocrine function owing to the relative radio-resistance of Leydig cells compared with germinal epithelium.
     - However, testosterone replacement therapy is ultimately required in 15% to 25% of patients undergoing RT.
  3) **Observation/deferred therapy**
     - Indicated for patients who desire future paternity but have abnormal or absent other testis, or have semen parameters that are abnormal but sufficient for assisted reproductive techniques.
     - Treatment can be deferred until successful pregnancy and/or GCT develops.
     - Other option in such patient is exploration of the testis, sperm harvesting and cryopreservation for ART, and radical orchiectomy followed by testosterone replacement therapy.

3. Tumour markers

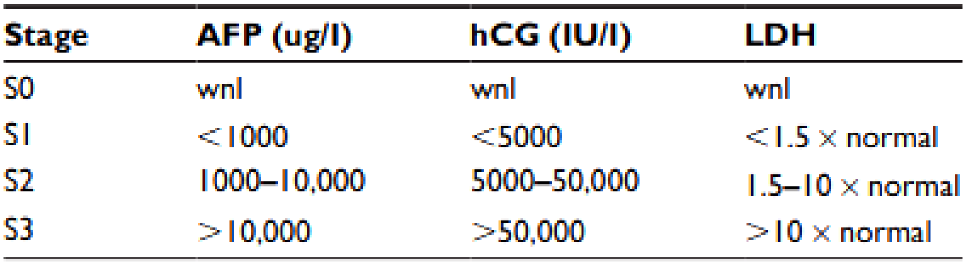
- For all patients undergoing orchiectomy for suspected testicular cancer, AFP, hCG and LDH should be measured. If levels are high before orchiectomy, they should be checked after orchiectomy after 4-5 weeks to find out if they are returning to normal.
- Tumor markers should not be used to make or change treatment decisions for **seminoma**.

	AFP	**HCG**	**LDH**
Structure	Glycoprotein- Single chain	Glycoprotein- A and β poly peptide chains	5 Types of isoenzymes LDH-1 & 2: Heart and RBCs LDH-3: LNs, lungs, platelets, pancreas LDH-4 & 5: Liver and skeletal muscle
Mol. weight	70 kDa	38 kDa	140 kDa
Half life	5-7 days	24-36 hours	24 hours
Elevation in GCTs	Elevated in 90% of NSGCTs	Elevated in 99% of Choriocarcinoma, and 10% of seminoma	LDH-1 is the most frequently elevated isoenzyme in GCT. Elevated in approximately 20% of low stage GCTs and 20% to 60% of advanced GCTs.
Significance in GCTs	Elevated AFP in GCTs→ treat like NSGCT Pure choriocarcinoma and pure seminoma do not produce AFP	Very high levels (>5000) almost always seen in choriocarcinoma. In seminoma usually levels are <500.	Main use is in the prognostic assessment of GCT at diagnosis. The magnitude of LDH elevation correlates with the bulk of disease burden
Elevated levels	Ca of Liver, stomach, pancreas, biliary tract, and lung. Patients with non-malignant liver disease (infectious, drug induced, alcohol-induced, autoimmune) Ataxic telangiectasia and hereditary tyrosinemia.	Cancers of the liver, biliary tract, pancreas, stomach, lung, breast, kidney, and bladder. Primary hypogonadism Marijuana	LDH is expressed in smooth, cardiac, and skeletal muscle. Lymphoma may also cause elevated LDH levels. Diseases of muscles, cardiac diseases, tissue death, hemolysis, high tissue turnover, and liver disease.

- **Tumor markers in different GCTs**

Seminoma	AFP (0), HCG (10%)
Yolk sac tumor	AFP (90%), HCG (0)
Embryonal carcinoma	AFP (rare), HCG (rare)
Teratoma	AFP (25%)
Choriocarcinoma	AFP (0%), HCG (99%)

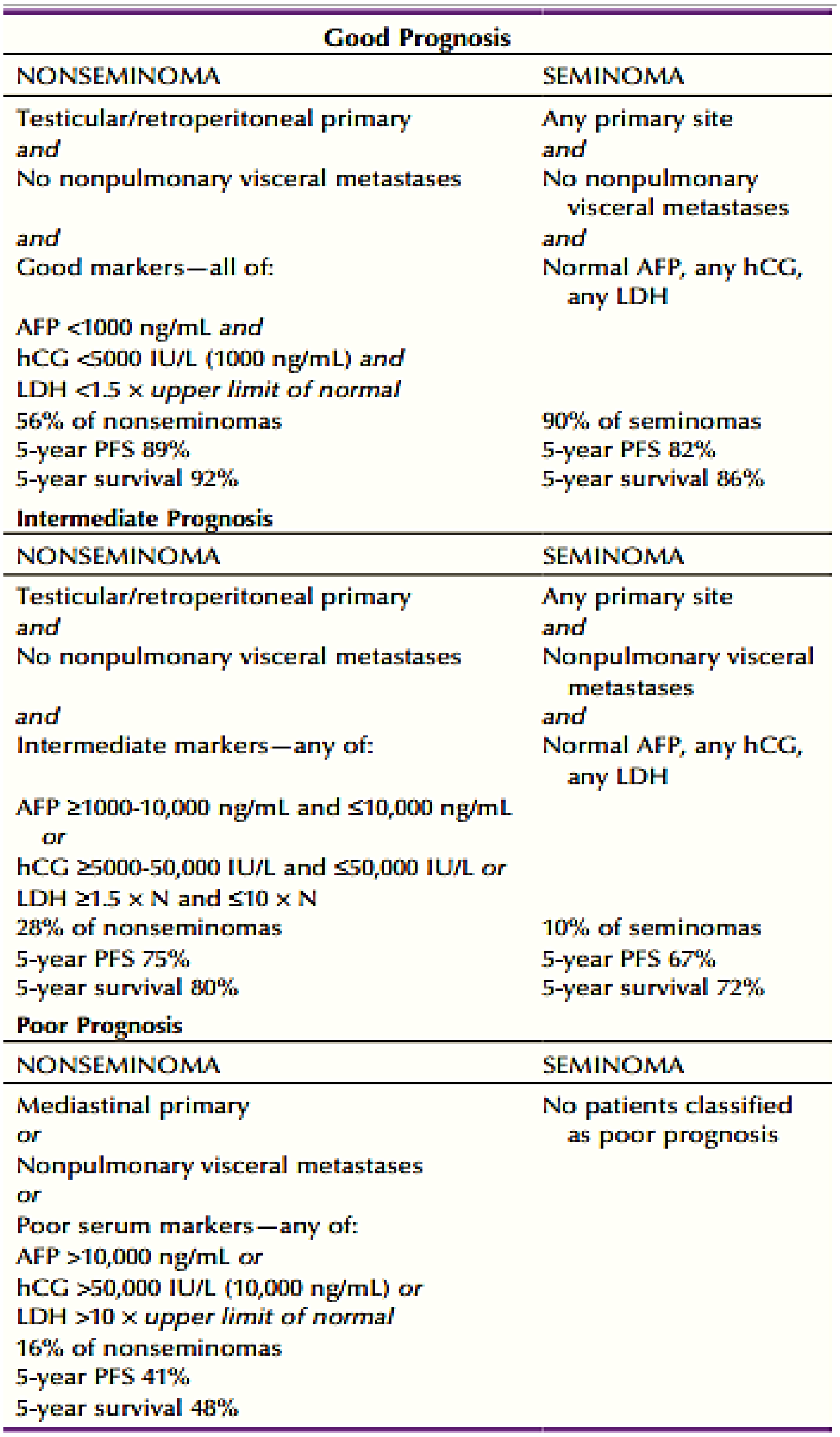
- **Tumor marker in clinical staging (Post-orchiectomy)**



Stage	AFP (ug/l)	hCG (IU/l)	LDH
S0	wnl	wnl	wnl
S1	<1000	<5000	<1.5 × normal
S2	1000–10,000	5000–50,000	1.5–10 × normal
S3	>10,000	>50,000	>10 × normal

4. Metastatic NSGCT- Risk stratification and management (essay)

- **International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification for Advanced GCT**
  - IGCCCG risk classification is used to evaluate the prognosis of patients with metastatic GCT and dictates the selection of chemotherapy.
  - For NSGCT, IGCCCG risk is assigned based on the post-orchiectomy tumor marker levels, mediastinal primary tumor, and the presence of non-pulmonary visceral metastases.
  - For seminoma, IGCCCG risk is assigned based on the presence of non-pulmonary visceral metastases only.

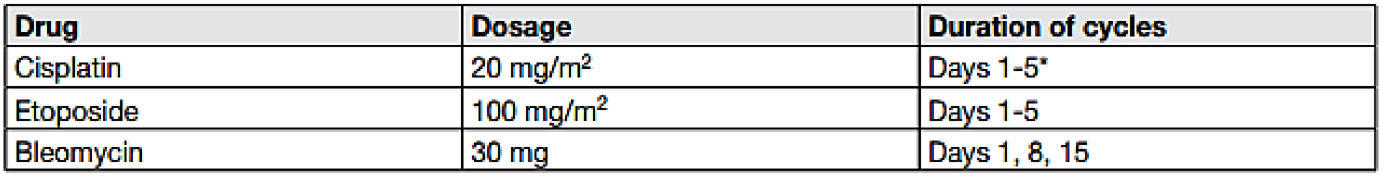


Good Prognosis	
NONSEMINOMA	SEMINOMA
Testicular/retroperitoneal primary *and* No nonpulmonary visceral metastases *and* Good markers—all of: AFP <1000 ng/mL *and* hCG <5000 IU/L (1000 ng/mL) *and* LDH <1.5 × *upper limit of normal*	Any primary site *and* No nonpulmonary visceral metastases *and* Normal AFP, any hCG, any LDH
56% of nonseminomas 5-year PFS 89% 5-year survival 92%	90% of seminomas 5-year PFS 82% 5-year survival 86%
Intermediate Prognosis	
NONSEMINOMA	SEMINOMA
Testicular/retroperitoneal primary *and* No nonpulmonary visceral metastases *and* Intermediate markers—any of: AFP ≥1000-10,000 ng/mL and ≤10,000 ng/mL *or* hCG ≥5000-50,000 IU/L and ≤50,000 IU/L *or* LDH ≥1.5 × N and ≤10 × N	Any primary site *and* Nonpulmonary visceral metastases *and* Normal AFP, any hCG, any LDH
28% of nonseminomas 5-year PFS 75% 5-year survival 80%	10% of seminomas 5-year PFS 67% 5-year survival 72%
Poor Prognosis	
NONSEMINOMA	SEMINOMA
Mediastinal primary *or* Nonpulmonary visceral metastases *or* Poor serum markers—any of: AFP >10,000 ng/mL *or* hCG >50,000 IU/L (10,000 ng/mL) *or* LDH >10 × *upper limit of normal* 16% of nonseminomas 5-year PFS 41% 5-year survival 48%	No patients classified as poor prognosis

- **Management of metastatic GCT**
  - First-line treatment of metastatic germ cell tumours is mainly systemic chemotherapy which depends on
    - Histology of the primary tumour
    - Prognostic groups as defined by the IGCCCG
  - **First line chemotherapy (Table)**

Risk group	Metastatic Seminomatous GCT	Metastatic NSGCT
Good	• Cisplatin-based regimen is preferred to carboplatin chemotherapy. • Standard treatment→ BEP x 3 or EP x 4 (in case bleomycin is contraindicated). EP x 4 results in cure in almost all cases of good-prognosis Seminomatous GCTs. • OS with EP x 4 for patients with good prognosis patients with metastatic seminoma is 99%.	• BEP x 3 is the primary treatment, which is superior to cisplatin, vinblastine and bleomycin (PVB). • EP x 4 (in case bleomycin is contraindicated) is other option but unlike seminomatous GCT, results are somewhat inferior to BEP in metastatic NSGCT.
Intermediate	• BEP x 4 or Etoposide, cisplatin, ifosfamide (VIP/EIP) x 4 (in case bleomycin is contraindicated) • OS with VIP x 4 for patients with intermediate prognosis patients with metastatic seminoma is 87%.	• BEP x 4 is the standard treatment. • Five-year survival rate is about 80%.
Poor		• BEP x 4 is the standard treatment. • Etoposide, cisplatin, and ifosfamide (EIP) x 4 have the same effect, but is more myelotoxic. • Five-year PFS is 45%-50%. • High-dose or dose-dense intensified chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline. • Thus, patients with an unfavourable tumour marker decline after BEP x 1 should be switched to a more intensive chemotherapy regimen.
		•

- **Drugs and basic regimen (Interval 21 days)**



Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

(* Always combine I/V hydration with Cisplatin)

- **Salvage chemotherapy for relapse or refractory disease**
  - Cisplatin-based combination salvage chemotherapy will result in long-term remissions in about 50% patients who relapse after first-line chemotherapy.
  - Regimens of choice are:
    - 4 x EIP/VIP
    - 4 x TIP (cisplatin, ifosfamide and paclitaxel)
    - 4 x GIP (cisplatin, ifosfamide and gemcitabine)

- **Second relapse**
  - Conventional therapy does not appear to be very effective.
  - High-dose (HD) chemotherapy with autologous stem cell support should be used
  - With HD-therapy the chance of cure is only 20-25%

- **Management of residual mass post-chemotherapy**
  - **Seminoma**
    - In patients with residual mass of > 3 cm post-chemotherapy, FDG-PET should be performed. Active masses should undergo surgical resection.
    - Extremely difficult surgery remove due to intense fibrosis

  - **NSGCT**
    - Following first-line BEP chemotherapy, only 6-10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue.
    - FDG-PET is not indicated to re-stage NSGCT patients after chemotherapy
    - Residual tumour resection (RPLND) is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging. In patients with residual lesions < 1 cm, there is still a risk of residual cancer or teratoma although majority (> 70%) of these harbour fibro-necrotic tissue only. Recurrence rate in patients with residual mass <1 cm is 6-9% depending on the time of follow-up (life-long risk of about 10%).
    - After salvage (2nd line) chemotherapy or high-dose chemotherapy, chances of vital tumour in the retroperitoneum is much higher. In these patients, RPLND is indicated even with residual disease < 1 cm.
    - RPLND should be complete, and all areas of primary metastatic sites must be completely resected within two-six weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed.

- **Desperation surgery**
  - Desperation surgery refers to resection of non-responsive or progressive (e.g. rising markers) disease following salvage (2nd line) chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term.

5. Testicular microlithiasis (TML)

- **Definition of TML**
  - TML is a condition in which calcium deposits form in the lumina of seminiferous tubules or arise from the tubular basement membrane components. It is a radiological and/or histological diagnosis.
  - On USG TML is typically seen as "innumerable tiny bright echoes diffusely and uniformly scattered throughout in the substance of testes"
- **Incidence**
  - On autopsy studies= 0.04-11.8% of prepubertal boys 3% of adult males
  - Population prevalence 5.6%

- **Ultrasound diagnostic criteria**
  - Greater than five calcifications per image field
  - Calcifications less than 2 mm in diameter
  - Diffuse in nature
  - No acoustic shadowing
  - No loss of testicular shape or volume.
- **Grading of TML**
  - Depending on the microliths count as seen in any single view of USG
    - Minimal/mild (Grade I: 5 to 10 microliths)
    - Moderate (Grade II: 10 to 20 microliths)
    - Severe (Grade III: >20 microliths)

- **Significance of Testicular microlithiasis**
  1) TML detected on routine USG does not warrant biopsy.
  2) **Infertility**
     a. Frequency of TML in patients with infertility or UDT: 7-39%
     b. Causes of decreased fertility in TML
        i. Mechanical obstruction of seminiferous tubules with microliths
        ii. Atrophy of uninvolved tubules with spermatogenic arrest
     c. Incidental discovery of TML should not change the treatment of infertility

3) TML has been linked to a common developmental defect of seminiferous tubules and defined as part of the **"Testicular dysgenesis syndrome"** which include testicular cancer, genital abnormalities, sub-fertility and reduced sperm quality.
4) **TML and malignanacy**
   - There is 40-fold higher prevalence of CIS/ITGCN in men with bilateral TML compared to those without TML (20% vs. 0.5%).
   - Biopsy should only be done if detection of CIS will be followed by treatment.
   - Indications of biopsy / Risk factors that warrant biopsy and/or follow-up of men with TML
     - i. Previous H/O GCT
     - ii. History of GCT in first degree relative
     - iii. History of UDT or orchidopexy
     - iv. Atrophy <12 ml (normal 12-30 ml, mean-18 ml)
   - If testicular malignancy is ruled out on the first evaluation/biopsy, TML can be followed up with regular self-examination of testes. If any change is noted by the patient, serum markers may be performed, and if elevated, biopsy can be done to rule out CIS or tumor provided there is intent to treat.

6. Yolk sac tumour (YST/EST)

- **Aka:** Endodermal sinus tumor, adenocarcinoma of the infantile testis, juvenile embryonal carcinoma, and orchioblastoma
- **Testicular YST** is the most common childhood testicular tumour (80%), with most cases occurring before the age of two years. In adults, pure YST, however an element of YST is found in mixed GCT in adults.
- **Cells of origin:** Totipotent cells, which later form extra-embryonic fetal membranes, give rise to yolk sac tumours.
- **Presentation**
  - Painless hard enlargement of a previously normal testis is the most frequent presentation
- **Markers**
  - AFP is elevated in >90% cases of YST.
- **Radiographic features**
  - Heterogeneous, hypoechoic testicular mass favours NSGCT, and at age <2 years, YST is the favoured diagnosis.
  - USG→ shoes diffusely enlarged heterogeneous testis
  - MRI→ Heterogeneous testicular mass lesion with post-contrast heterogeneous enhancement, with areas of hemorrhage/necrosis
- **Pathology**
  - Grossly, YST is solid gray-white with testis replaced by a gelatinous or mucoid mass. Necrosis, cystic changes, and hemorrhage are often seen. In adults, overall appearance of a yolk sac tumor (YST) is heterogeneous.
  - Microscopically, perivascular structures called Schiller-Duval bodies can be found in 50% of tumours and are pathognomonic. YST is positive for AFP staining. Cytokeratin is present in almost all the cases. Approximately 40-80% of cases are positive for PLAP.
  -
- **Treatment and prognosis**
  - High inguinal orchiectomy is complete treatment for Stage I disease, with close follow-up.
  - Chemotherapy followed by RPLND is indicated for Stage II and III. BEP is the standard chemotherapy.
  - Stage I patients with slow fall of AFP to normal (>18 months) should be treated like Stage II.
  - If relapse occurs, chemotherapy is the treatment of choice.
  - The lungs are most common site of recurrence.
  - Long-term follow-up (>48 month) is recommended.

Prostate Benign

1. TUR syndrome

- TUR syndrome occurs in 2% of the patients and is associated with a 18% mortality.
- The syndrome was characterized by mental confusion, nausea, vomiting, hypertension bradycardia, and visual disturbance.
- There is dark red discoloration of the serum, progressive oliguria, azotemia, and pulmonary edema, followed by death.
- Usually, the patients do not become symptomatic until the serum sodium concentration reaches 125 mEq/dL.

The amount of fluid absorbed is directly related to
(a) the pressure of the irrigant, which is a function of the height the bag is placed above the prostatic fossa
(b) the intravesical pressure
(c) the intraprostatic pressure
(d) the CVP.

- The duration of the resection, the size of the gland, the quality of resection, and the type of resection, and equipment used also play a role.
- The risk is increased if the gland is larger than 45 g and the resection time is longer than 90 minutes.
- As a rule, 20 mL per minute of fluid are absorbed and 2 mL per minute of blood are lost during resection. In TURP approximately 1000ml of fluid was absorbed by the patient. When the height of the fluid was changed from 60 to 70 cm, fluid absorption was greater than twofold.
- Also approximately 300 mL/min of fluid was needed for a good vision field and this could not be achieved when the fluid level was below 60 cm H2O.
- TUR syndrome is secondary to dilutional hyponatremia.

Management

- one can attempt to calculate the amount of water overload by determining the serum sodium preoperatively and postoperatively, knowing the patient's weight, and determining the amount of extracellular fluid.
- Mixing 1% ethanol in turp irrigation fluid and subsequently measuring ethanol in breath, one can calculate the quatity of fluid absorbed.
- Treatment is by simultaneous administration of a potent diuretic, such as furosemide, with the restoration of serum sodium content by the infusion of hypertonic saline solution.
- The sodium deficit is calculated by subtracting the current serum sodium from the desired serum concentration and multiplying the value by the quantity 0.2 × body weight in kilograms (extracellular fluid volume).
- If the patient has neurologic symptoms or signs, 3% sodium chloride is used. On the other hand, if neurologic abnormalities are absent, normal saline may be used.

- This can be done by approximately giving the patient 200 mL of 3% saline solution very slowly over a period of time.
- During intraop, serum sodium is measured and when patients demonstrate a drop in serum sodium level, diuretics (e.g., furosemide [Lasix]) are administered. The serum sodium concentration is measured in the postoperative recovery area, and, if need be, a further dose of diuretic is administered.

2. Natural history and principles of medical management

The natural history of BPH can theoretically be evaluated by studies of a variety of designs:

- Longitudinal studies of untreated cohorts of men diagnosed with LUTS and clinical BPH by any definition (*watchful waiting cohorts*)
- Studies of the behavior of men diagnosed with LUTS and BPH and enrolled in controlled studies of LUTS and BPH (*control groups*) and receiving either
  - *no treatment* (compared to active intervention),
  - *placebo* treatment (compared to medical treatment), or
  - *sham* treatment (compared to device or surgical treatment)
- Longitudinal studies of unselected (i.e., undiagnosed) men living in the community who are less likely to progress and request or require therapy (*longitudinal population-based studies*)

LUTS associated with BPH is an increasingly prevalent condition in ageing men, which significantly affects their daily life. Although BPH is not a life-threatening condition, some men with LUTS have a progressive disease, which is defined -

- deterioration of symptoms and health-related quality of life
- decreased peak flow rate
- increased prostate size
- acute urinary retention (AUR)
- BPH-related surgery

LONGITUDINAL COMMUNITY-BASED STUDIES

1) OLMSTED COUNTY STUDY

For 12 years a randomly selected cohort of 2115 men aged 40–79years recruited/followedup.

Results

- the severity of LUTS increased and the peak flow rate decreased, with time and age
- **Mean increase in the IPSS of 0.18 points per year** (95% CI 0.13–0.24)
- Annual increase in IPSS was low (0.14) in men aged 70–79 years,
- **Decrease in median peak flow rate of 2% per year** that was also age-related, with men aged ≥70 years showing a more rapid decline than men in their fifties.
- Prostate growth increased with time by a **median of 1.9% per year**
- The cumulative incidence of **AUR was 2.7% over 4 years**

- 3% of men had TURP or a minimally invasive surgical procedure during a 6-year follow-up, and this was again strongly age-related .

2) HEALTH PROFESSIONALS FOLLOW-UP STUDY

- Prospective cohort study analysed the incidence of AUR among 6100 health professionals aged 45–83 years who(questionnaire based) had no history of prostate cancer, prostatectomy or AUR.
- The duration of follow-up was 3 years.
- The incidence of AUR was 1% over 3 years, ranging from 0.2% in men aged 40–49 years to 3% in men aged>80 years.

CONTROLLED STUDIES

1) PROSCAR LONG-TERM EFFICACY AND SAFETY STUDY (PLESS)

- Assess the long term benefit of finasteride in symptomatic BPH
- Randomized; 3040 men; Finasteride vs placebo for 4 years

Results:

Finasteride group

- 57% relative risk reduction for AUR
- 55% RR reduction for surgical intervention

2) MEDICAL THERAPY OF PROSTATIC SYMPTOMS (MTOPS) STUDY

- Assess the importance of medical therapies on the risk of BPH progression
- 5 yrs, > 3000 men over 50yrs, mod. to severe LUTS , Q max 4 – 15 ml/s)
- Primary end point: 1st occurrence of clinical progression event

Results:

Symptom deterioration(IPSS worsening by 4 points) – most common progression event

Cumulative clinical progression:

- 17% - Placebo, 10% - alpha blocker, 10% - 5 ARI, 5% - Combination therapy.

Combination therapy:

- Reduces The long term risk of AUR
- Need for invasive therapy

Progression of LUTS is predictable

- ↑ Larger prostates (& higher PSA)
- Combination therpy reduces risk of progression; maximally for those at highest baseline risk.

3) ALFUZOSIN 10 mg ONCE DAILY LONG-TERM EFFICACY AND SAFETY STUDY (ALTESS)

- Impact of alpha blockers on men with high risk of progression
- Double binded, placebo controlled; 1522 men over 2 years.
- Primary end point: 1st AUR or BPH related surgery

Results:

Placebo –incidence of

- Symptom deterioration (IPSS>4) – 16.8%
- AUR – 2.1 %
- BPH related surgery – 6.5%

Alfuzosin – Incidence of

- Symptom deterioration – 11.7%
- AUR – 1.8 % (not significant)
- BPH related surgery – 5.1%
- Reduces symptom deterioration and thus clinical progression
- Does not significantly reduce the incidence of AUR
- Reduces the risk of BPH related surgery

Principles of medical management-

- Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.
- The exact etiology is unknown; the similarity between BPH and the embryonic morphogenesis of the prostate has led to the hypothesis that BPH may result from a "reawakening" in adulthood of embryonic induction processes
- The enlarged gland contributes to the overall lower urinary tract symptoms (LUTS) complex via two routes
  1. direct bladder outlet obstruction (BOO) from enlarged tissue (static component)
  2. from increased smooth muscle tone and resistance within the enlarged gland (dynamic component)
- Traditionally, the primary goal of treatment to alleviate bothersome LUTS that result from prostatic enlargement the alteration of disease progression and prevention of complications that can be associated with BPH/LUTS.

MEDICAL TREATMENT OF OBSTRUCTIVE BPH
Indication

1.Mild IPSS (symptom score)
2. Moderate to severe symptoms initially
3.Individual who lacks absolute indication for surgery

Drugs available:

1. alpha adrenergic blockers
2. androgen manipulation
3. Combination therapy → alpha blocker + 5alpha reductase inhibitor
4. Anticholinergic blockers → LUTS
5. Phosphodiesterase inhibitor → LUTS
6. Phyto therapy

1.alpha adrenergic blockers :classification

a. Nonselective: → Phenoxybenzamine 10mg bd
b. alpha 1 → Prazosin 2mg bd
  → IR Alfluzosin 2.5mg bd
  → Indormin
c. long acting alpha 1 → Terazosin 5mg od
  → Doxazosin 4-8mg od
  → Alfuzosin SR 10mg od

d. Subtype selective → Tamsulosin =0.4mg od
  → Sitodoxin 8mg od
  → Naftopidil

2. Androgen manipulation: --blockage of DHT

a.Cyproterone acetate
b.5 alpha reductase inhibitor → Finasteride (type ii) 5mg od
prostate volume regression maximum 50% at 6 months
c.Dutasteride → (type 1&2) 0.5mg /day
d. Zanoterone :steroidal competitive androgen receptor antagonist =200mg/day
e.Flutamide
f. cetoredix
g.Aromatase inhibitor → Atamertane 400mg

PHYTOTHERAPY:

1.Serenra reopens Saw palmetho
2.Pygeum africanum

Remember - Predictors of poor outcome with medical therapy-

- Age >65 years
- Enlarged prostate (volume >30ml)
- Increased serum PSA (≥1.5ng/ml)
- High post void residual urine (PVR>50ml)
- Baseline LUTS severity (IPSS >7)
- Low peak flow rate (<12ml/sec)
- Intravesical protrusion (>1.0cm)

3. Management of spontaneous prostate related bleeding (essay) –

Key Words: prostate, prostatitis, prostatic neoplasms, prostatic hyperplasia, urethra hemorrhage

INTRODUCTION

Spontaneous hemorrhage is a clinically important manifestation of prostate disease. **Patients with any 1 of the 3 significant prostate diseases, benign prostatic hyperplasia (BPH), prostate cancer and/or prostatitis, may present with spontaneous bleeding at various stages of the disease. In turn, prostate related bleeding may manifest clinically as gross hematuria, hematospermia or urethral bleeding.**

We describe the epidemiology, explain what we know about the etiology, outline a diagnostic strategy and attempt to provide a ''best'' evidence based algorithm for the management of spontaneous prostate related bleeding. We will not address prostate related bleeding following biopsy, prostate surgery, trauma, endoscopy or catheterization. Discussion has been structured according to prostate cancer, BPH and prostatitis. Management options are outlined and a hematuria management algorithm is presented.

EPIDEMIOLOGY

Gross hematuria is a relatively common presentation in older men. Hunter et al noted that 2.5% of 2002 Spanish men older than 50 years reported hematuria,[1] while Han et al described hematuria in 0.7% of 26,126 American men older than 40 years.[2] Hematospermia appears to occur as a presenting complaint in almost as many men (0.5% of the study population of Han et al[2]). To our knowledge, epidemiological data on the incidence of spontaneous urethral bleeding are unavailable. **It has been reported that ''BPH is the most common cause of gross hematuria in men older than 60 years.''**[3] Gross hematuria was an indication for transurethral resection of the prostate (TURP) in 12% of patients in 1 large series.[4] Urethral bleeding without gross hematuria is also a frequent cause of alarm in patients with BPH but is believed by most urologists to have a more benign course.

Gross hematuria with urethral bleeding is an infrequent, nonspecific symptom occurring in patients with prostate cancer[5] and occasionally can be a difficult management problem. **While it has always been believed that hematospermia was not associated with a diagnosis of prostate cancer, recent epidemiological evidence suggests a weak association of hematospermia in a population of men being screened for prostate cancer**.[2] In an epidemiological study of 1074 Italian men with prostatitis 15.7% reported hematospermia and 2.5% reported hematuria as presenting symptoms.[6]

ETIOLOGY

The pathophysiology of spontaneous prostate related bleeding is not completely understood. The mechanism may differ depending on the underlying prostate disease. In BPH spontaneous bleeding is likely related to increased vascularity within hyperplastic prostate tissue as well as abnormal, friable prostate tissue exposed in the prostatic urethra.[7] Microvessel density is higher in prostate tissue from men with BPH,[8] and particularly in men with BPH and hematuria.[9] **The increased vascularity within prostate tissue seen in men with BPH is at least partly related to increased expression of vascular endothelial growth factor (VEGF).**[7,10]

The mechanism by which spontaneous bleeding occurs in men with prostate cancer is probably similar, although less well characterized. The histological and immunohistochemical findings seen in BPH (increased microvessel density and VEGF expression) are also observed in prostatic adenocarcinoma.[10-12] The pathophysiology of spontaneous bleeding in men with prostatitis is not as well understood. Hypotheses regarding other inflammatory conditions associated with bleeding, such as pancreatitis, include vessel erosion etc but this has never been shown to be the case for prostatitis. Prostatic inflammation (either bacterial or nonbacterial) may increase the risk of spontaneous bleeding but this is speculative.

DIAGNOSIS

Before the etiology of hematuria, hematospermia or urethral bleeding can be assigned a prostate related diagnosis, all other causes of urinary tract hemorrhage must be ruled out. Every standard urology textbook has detailed recommendations for the evaluation of patients presenting with hematuria.[13] The American Urological Association has developed guidelines for the evaluation of men with microscopic hematuria.[14] The assessment of hematuria in patients with an underlying prostate disease should not be substantially different. A suggested stepwise diagnostic strategy starting with history and physical examination, proceeding to urine studies and then endoscopy and upper tract imaging is shown in Appendix 1.

Urethral bleeding does require further investigation and cannot be assigned a prostate related etiology by history alone. As described in Appendix 2, endoscopy is necessary but upper tract imaging is not required unless hematuria is noted between episodes of urethral bleeding. If this is impossible to determine (for example, in patients in whom urethral bleeding is a persistent occurrence), then upper tract imaging studies should be performed Occassionally imaging of the prostate and related structures with transrectal ultrasonography (TRUS), magnetic resonance imaging (MRI) or even voiding cystourethrography may be helpful.

Hematospermia has usually been accepted as a benign condition. However, before such a conclusion can be made, some investigations are indicated. Concurrent hematuria (gross or microscopic) must be ruled out by careful history, physical examination including digital rectal examination (DRE) and urinalysis. The requirement for further studies is controversial but many clinicians believe that it is important to completely rule out all other pathology to account for the hematospermia (Appendix 3).[15-17] We suggest a serum prostate specific antigen (PSA) measure and urine cytology (in men older than 40 years). Cystourethroscopy is usually not rewarding and not recommended, but many proceed with this investigation as it can be reassuring for the urologist and patient. Seminal vesicle endoscopy has even been recommended in select cases of hematospermia.[18] Transrectal ultrasound (or pelvic MRI) can be used to determine if the hematospermia is related to prostate calculi or cysts and seminal vesicular or ejaculatory duct abnormalities.[19-22] The differential diagnosis of hematospermia is shown in Appendix 4. Only if all investigations in Appendix 3 are negative (and they usually are) can the diagnosis of hematospermia be assigned to an underlying prostate (or related structure) pathology.

MANAGEMENT

Treatment strategies for prostate related bleeding. There are no clinical trial data in the literature on which to develop a true evidence based treatment algorithm for prostate related bleeding. However, at the Queen's University Department of Urology we base our management strategy on the best evidence available in the literature, anecdotal reports, clinical experience and intuition. It is up to each individual urologist to develop his or her own management algorithm based on their training, experience, facilities and personal interpretation of the literature.

Life threatening hemorrhage. **The first step in treating any patient with hemorrhage of any source is to ensure hemodynamic stability.** While hematospermia and urethral bleeding are usually not an acute emergency, prostate related gross hematuria can be life threatening. In those patients it is important to verify stable vital signs, adequate hemoglobin (hematocrit) levels, normal coagulation parameters and acceptable renal function. Reversal of anticoagulation with vitamin K may be indicated. Acute spontaneous prostate related bleeding can quickly progress to painful clot retention necessitating a rapid response by the medical staff. Prompt establishment of intravenous catheter(s) and fluid resuscitation, monitoring and transfusion of blood products may be necessary if the patient is unstable or coagulopathic.

Good urinary tract drainage is essential. Hemodynamic support should be followed promptly by catheterization and clot evacuation. Various techniques and catheters have been developed but suffice it to say that all urologists appreciate that a wide bore stiff catheter and vigorous manual irrigation are required. Once the clots have been evacuated (**all clot material must be removed from the bladder or the bleeding will continue and the clot will reform and enlarge**), a standard 22 to 26Fr 3-way Foley catheter should be inserted and the patient carefully monitored as an inpatient with continuous bladder irrigation until the bleeding resolves. If this is unsuccessful or if the bleeding cannot be controlled, the diagnostic steps suggested in Appendix 1 should be bypassed, and the patient should be taken directly for endoscopic treatment. Such urgent treatment might consist of electric or laser cauterization or even a limited TURP once the source of the bleeding is confirmed to be the prostate gland.

Gross hematuria related to BPH. Once the source of hematuria has been confirmed to be BPH, the best treatment may be reassurance, increased hydration, watchful waiting and, if indicated, adjustment of medication that may be implicated (eg warfarin or coumadin, acetylsalicyclic acid or other antiplatelet agents) However, in many cases the hematuria is refractory or recurrent. **The most extensively studied intervention in the management of hematuria is the use of finasteride for recurrent or refractory BPH related bleeding. Treatment with finasteride appears to reduce prostatic blood flow measured by Doppler TRUS,[23] prostatic microvessel density[7,24] and VEGF expression.**[7] A number of retrospective[25,26] and uncontrolled[27-30] data suggest that finasteride therapy significantly reduces the frequency and severity of BPH related bleeding. The reported response rates range from 86% to 100%.

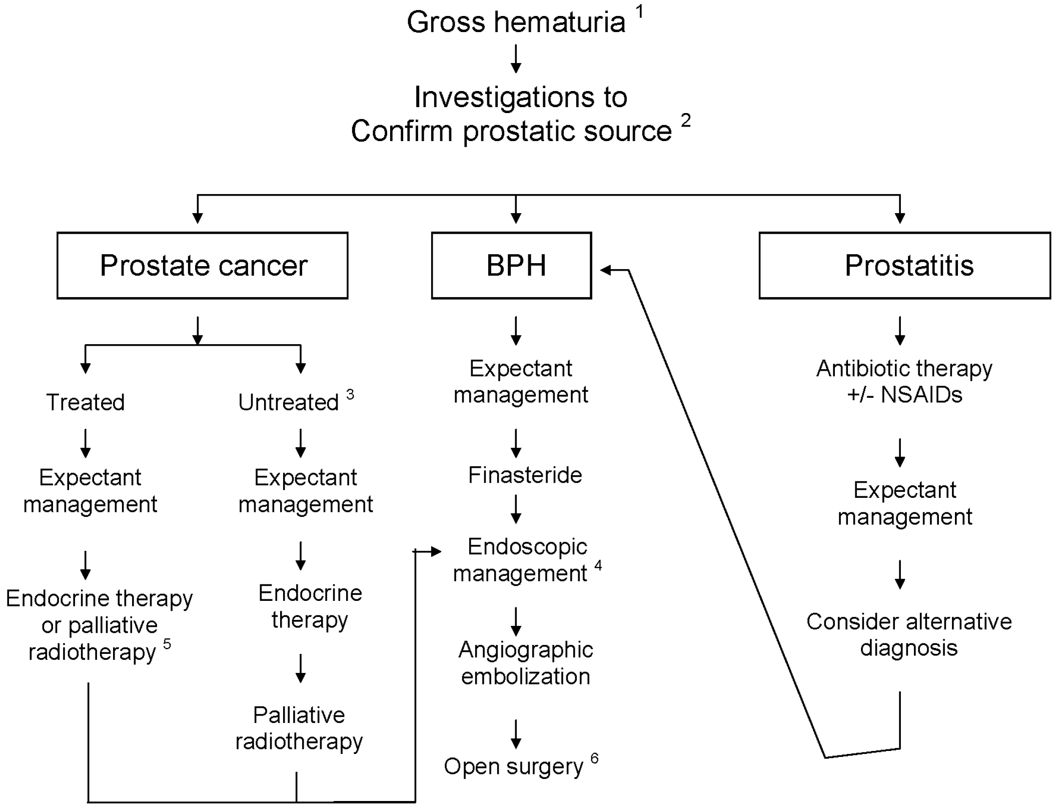
Foley et al prospectively randomized 57 patients with BPH related bleeding to 5 mg finasteride daily or watchful waiting for 12 months.[9] In each group approximately two-thirds of the men had previously undergone prostate surgery. Hematuria recurred in 63% of untreated control patients vs 14% of finasteride treated patients. Surgery for the BPH related hematuria was required in 26% of untreated control patients vs none in the finasteride group. Perimenis et al prospectively randomized 42 patients with BPH related gross hematuria to finasteride, cyproterone acetate and watchful waiting for 12 months.[31] Of the watchful waiting arm 57% experienced recurrent bleeding, and half of these patients required either catheterization or TURP to manage it. None of the patients treated with finasteride or cyproterone required any intervention for recurrent hematuria. Although there was no statistically significant difference in bleeding recurrence at 3 and 6 months, by 9 and 12 months the incidence of hematuria was significantly lower in the finasteride and cyproterone arms of the study. Finasteride and cyproterone were equally effective at reducing bleeding, which suggests a class effect, and that other 5-alpha reductase inhibitors (dutasteride) and antiandrogens (flutamide and perhaps even estrogens) may be useful in the setting of BPH related bleeding.

Recent data have also attempted to identify factors that predict response to finasteride therapy. Prostate size does not appear to predict whether patients will respond, as in a recent uncontrolled clinical trial those with large and small prostates were equally likely to experience resolution of prostate related bleeding.[32] However, Kearney et al found that larger prostate glands may take longer to stop bleeding, and the time to resolution was proportional to prostate size.[33] These authors also noted that gross hematuria responds well to finasteride therapy even in patients who have previously undergone TURP or are anticoagulated. Patients who have symptomatic BPH and gross hematuria should be considered for prostate related surgery, either TURP or simple open prostatectomy. There is little experience to determine the efficacy of minimally invasive surgical treatments for BPH related hematuria. Occasionally even TURP is unsuccessful and significant bleeding recurs.

The use of antifibrinolytic agents (eg epsilon aminocaproic acid) has been suggested for cases that fail endoscopic surgery and medical therapy.[34] Epsilon aminocaproic acid is a potent competitive inhibitor of activators of plasminogen, including urokinase. When given orally or intravenously 80% of the drug is excreted unchanged in the urine within 24 hours. Several trials suggest a 50% reduction in blood loss following elective prostate surgery when patients are treated with antifibrolytic agents.[35,36] However, there are no data available which specifically examine the use of antifibrinolytics in patients with refractory BPH related bleeding. Clinical trials have not documented an increase in thrombotic events (eg stroke, myocardial infarction) with the use of these agents, although they may not have been powered to do so.[37] **These agents should be used with care owing to the lack of evidence supporting their use in this situation and the theoretical risks inherent with their use.**

Patients in whom hematuria persists despite medical and surgical measures may have to be considered for repeat fulguration. **If repeated attempts at endoscopic management are unsuccessful, heroic measures may be necessary, possibly including angiographic arterial embolization,[38,39] radical prostatectomy and even urinary diversion.** The figure outlines a suggested treatment algorithm for BPH related hematuria.

Gross hematuria related to prostate cancer. **Patients with untreated prostate cancer should be considered for specific prostate cancer therapy (radical prostatectomy, radiotherapy, hormonal therapy) which usually controls the prostate related bleeding**. Mild recurrent hematuria in patients treated for prostate cancer can be watched carefully unless the bleeding becomes problematic. For patients who continue to bleed despite local radiotherapy and/or hormone therapy, endoscopic fulguration, limited TURP



Treatment algorithm for prostate related gross hematuria. *1*, hemodynamically stable patient. *2,* see Appendix 1. *3,* in a patient for whom immediate radical therapy (radical retropubic prostatectomy, radiotherapy) is not desirable or appropriate. *4,* repeated attempts at endoscopic management may be appropriate in many cases (TURP, fulguration). *5,* based on clinical situation (eg treatments already used). *6,* last resort (radical or salvage prostatectomy, cystectomy, urinary diversion).

or in the worst-case scenario salvage prostatectomy can be considered. Radiation-induced hemorrhagic cystitis is a diagnostic consideration in such patients as well, and it is important to differentiate between this and actual prostate related bleeding, especially when bleeding is refractory to treatment directed at a prostatic source (eg hormonal therapy).

Therapy with antifibrinolytic agents (eg epsilon aminocaproic acid) has been suggested for patients with prostate cancer related bleeding, and older literature attests to its possible benefits.[40] As suggested previously, **theoretical complications of antifibrinolytic therapy should be balanced against the limited evidence of benefit.** A number of intravesical therapies advocated for hemorrhagic cystitis have been used for gross hematuria related to prostate cancer but the evidence is sparse. These include alum irrigation[41] and formalin instillation.[42] Hyperbaric oxygen therapy has been suggested as helpful in cases of refractory hemorrhagic cystitis[43-46] but its role in the setting of refractory prostate cancer related bleeding would be speculative.

Gross hematuria related to prostatitis. **Hematuria associated with inflammatory prostatitis should be managed with antibiotic therapy (an argument can be made to treat patients with non-bacterial prostatitis and hematuria with antibiotics even if the urine culture is negative).** Prostatitis related bleeding is rarely life threatening and usually self-limited, seldom requiring endoscopic management.

Urethral bleeding. **The initial episode of prostate related urethral bleeding does not usually require therapy unless profuse and continual.** In the finasteride trials described previously patients with urethral bleeding responded well to finasteride therapy.[25-30] Endoscopic fulguration may sometimes be required for patients with BPH and prostate cancer but rarely for those with prostatitis. TURP is indicated for BPH with significant and bothersome urethral bleeding refractory to medical therapy. Urethral bleeding usually resolves with treatment of associated prostate cancer, although radiotherapy can cause urethral bleeding that can be difficult to treat (but it is not usually that severe).

Hematospermia. **Most patients with hematospermia due to prostate causes can be managed expectantly with reassurance.** However hematospermia can be recurrent and quite profuse. If bothersome, finasteride may be effective for patients with BPH;[47,48] antibiotics, anti-inflammatories and perhaps finasteride for those with prostatitis; and endocrine manipulation for patients with prostate cancer. Surgery for hematospermia directly related to one of these prostate conditions is not recommended.

SUMMARY

Spontaneous prostate related bleeding has been investigated and treated by urologists for decades, yet little guidance on management is provided in the literature. Except for the use of finasteride for BPH related bleeding, clinical trials are sparse and the data required to provide an evidence based approach are not available. This lesson provides the foundation on which a urologist can develop his or her own management protocol based on best available literature, personal experience and local resource considerations.

APPENDIX 1: DIAGNOSTIC STRATEGY FOR PROSTATE RELATED HEMATURIA IN A PATIENT WITH A DIAGNOSIS OF BPH, PROSTATE CANCER OR PROSTATITIS

- History: age, smoking, medications (anticoagulants or antiplatelet agents), chemical exposure, lower urinary tract symptoms, microscopic hematuria (during times when gross hematuria resolves), urethral bleeding, hematospermia, urological history
- Physical examination: vitals, abdomen, genitalia, DRE
- Urine investigations: urinalysis, urine culture, urinary cytology
- Blood tests: PSA (except for bacterial prostatitis), coagulation studies
- Endoscopy: cystourethroscopy
- Imaging: ultrasonography, computerized tomography urography, excretory urography

APPENDIX 2: DIAGNOSTIC STRATEGY FOR PROSTATE RELATED URETHRAL BLEEDING IN A PATIENT WITH A DIAGNOSIS OF BPH, PROSTATE CANCER OR PROSTATITIS

- History: age, medications (anticoagulants or antiplatelet agents), lower urinary tract symptoms, hematuria, hematospermia, sexually transmitted disease, trauma, urological history
- Physical examination: vitals, abdomen, genitalia, DRE
- Urine investigations: urinalysis, urine culture, +/− urethral swabs, urine cytology
- Blood tests: PSA (except for bacterial prostatitis), coagulation studies
- Endoscopy: cystourethroscopy
- Imaging: see text

APPENDIX 3: DIAGNOSTIC STRATEGIES FOR PROSTATE RELATED HEMATOSPERMIA IN A PATIENT WITH A DIAGNOSIS OF BPH, PROSTATE CANCER OR PROSTATITIS

- History: age, isolated vs persistent hematospermia, ejaculatory pain, pelvic pain, lower urinary tract symptoms, hematuria, urethral bleeding, medications (anticoagulants or antiplatelet agents)
- Physical examination: abdomen, spermatic cords, external genitalia, DRE
- Urine investigations: urinalysis, urine culture (bacterial, +/− acid-fast bacilli if indicated), culture of expressed prostatic secretion and/or post-prostatic massage urine for prostatitis, urethral swabs for urethritis, urinary cytology, semen culture
- Blood tests: PSA (except for bacterial prostatitis), coagulation studies
- Imaging: see text

APPENDIX 4: DIFFERENTIAL DIAGNOSIS OF HEMATOSPERMIA

Idiopathic (most common)
Genital tract infection:
    Prostatitis (up to 30%)
    Urethritis (up to 7%)
    Epididymitis
    Other infections (TB, HIV, CMV, schistosomiasis, echinococcus)
    Funiculitis
Prostate cancer (2%)
Urethral cysts, polyps, condylomata acuminata (1.5%)
Urethral stricture (1.5%)
Prostatic varices
Prostatic calculi
Seminal vesicle cysts (congenital/acquired)
Seminal vesicle neoplasm
Trauma
Systemic disease (amyloidosis, coagulopathy, hypertension, lymphoma, liver disease)

Adapted from Schiff JD and Mulhall J: Hematospermia. Emedicine 2004; July 23 http://www.emedicine.com/med/topic3466)

*4. Stuck Foley's catheter- Causes and management

Various conventional methods available are:

- Ether technique - Banned due to ether chemical pyelitis
- Over filling and rapture of balloon - Banned due to residual balloon pieces in bladder and rarely rupture bladder
- Suprapubic puncture of balloon blindly or ultrasound guided
- Per rectal palpation of balloon and puncturing with needl
- Catheter telescopy for retrieval of impacted catheter
- Suprapubic cystostomy as the last resort to retrieve the catheter.

5. Bladder changes in Parkinsonism

Lower Urinary Tract Symptom

The reported prevalence of LUT symptoms (LUTS) in patients with PD ranges from 40 % to 70%.

Storage Symptoms

- Storage symptoms are the most common of the LUTS symptom types in PD. Storage symptoms include nocturia (nighttime urinary frequency) reported by patients with PD (>60%).
- Patients also complain of urinary urgency (30–50%) and daytime frequency (16–36%).
- Urinary incontinence was present in 26% of male and 28% of female patients with PD.

Voiding Symptoms

- PD patients had significantly higher rates of Hesitancy (45% of men only), prolongation/poor stream (70% of men only), and straining (30% of women only). However, despite the voiding symptoms, PD patients have low postvoid residuals .

Videourodynamics/Pressure-Flow Analysis/Sphincter Electromyography- Bladder (Detrusor) Overactivity —

- The storage-phase urodynamic abnormalities in PD include reduced bladder capacity together with detrusor overactivity (DO) in 45–95%.
- Uninhibited external sphincter relaxation in 35%of patients hence, DO can be the major contributing factor to overactive bladder in PD.
- Mild, Weak Detrusor, and Sphincter Obstruction — Pressure-flow analysis in PD has shown weak detrusor activity during voiding (40% of men; 66% of women).

Remember!!-

- The smooth sphincter is **synergic.**
- **Pseudodyssynergia** may occur, as well as a delay in striated sphincter relaxation **(bradykinesia)** at the onset of voluntary micturition, both of which can be urodynamically misinterpreted as true dyssynergia.
- **Impaired detrusor contractility** may also occur, either in the form of low amplitude or poorly sustained contractions or a combination.
- **Detrusor areflexia** is relatively uncommon in PD.

6. Non-surgical management of BPE –

1. **Medical Management**
2. **Intraprostatic Stents**
3. **Transurethral Needle Ablation of the Prostate**
4. **Transurethral Microwave Therapy**

1. Medical Management-

A. Alpha adrenergic blockers :classification

a. Nonselective:→ Phenoxybenzamine 10mg bd

b. alpha 1 → Prazosin 2mg bd
→ IR Alfluzosin 2.5mg bd
→ Indormin

c. long acting alpha 1 → Terazosin 5mg od
→ Doxazosin 4-8mg od
→ Alfuzosin SR 10mg od

d. Subtype selective →Tamsulosin =0.4mg od
→Sitodoxin 8mg od
→Naftopidil

B. Androgen manipulation: --blockage of DHT

a.Cyproterone acetate
b.5 alpha reductase inhibitor → Finasteride (type ii) 5mg od
prostate volume regression maximum 50% at 6 months
c.Dutasteride→ (type 1&2) 0.5mg /day
d. Zanoterone :steroidal competitive androgen receptor antagonist =200mg/day
e.Flutamide
f. cetoredix
g.Aromatase inhibitor → Atamertane 400mg

C. PHYTOTHERAPY:

1.Serenra reopens Saw palmetho
2.Pygeum africanum

		α1 subtype binding	Plasma half life (hrs)	Dosing	
				mg	times/day
1st generation *Both α and β receptors*	**Phenoxybenzamine**	α1 = α 2	intravenous; ~ 24 hrs	20 – 40	2 - 3
2nd generation *selective for α 1 receptors*	**Prazosin**	α1 a = α1 b = α1 d	2 - 3	10	2
	Doxasosin	α1 a = α1 b = α1 d	22	4-8	1
	Terazosin	α1 b = α1 d > α1 a	12	2 - 10	1
	Alfuzosin	α1 a = α1 b = α1 d	9	10	1
3rd generation *superselective for α 1 a /α 1 d receptors*	**Tamsulosin**	α1 a = α1 d > α1 b	9- 13	0.4 -0.8	1
	Silodosin	α1 a > α1 d >> α1 b	13	4 - 8	2
	Naftopidil	α1 d > α1 d > α1 b	3.3	25 - 75	1

2. Intraprostatic Stents

Temporary Stents

A. Spiral Stents

1. **First-Generation Stents.**
    - Urospiral and the ProstaKath
    - 21-Fr stainless steel
2. **Second-Generation Stents.**
    - Memokath and Prosta Coil
    - Nitinol, a nickel-titanium alloy, It permits the passage of a flexible cystoscope and may be left in place for up to 36 months.

B. Polyurethane Stents

Also known as intraurethral catheters, three types:

- Intraurethral catheter
- Barnes stent
- Trestle stent

C. Biodegradable Stents

- the stents do not need to be removed, and eventually they disappear by biodegrading into small fragments of polymer debris that were passed out in the urine.
- voiding became more obstructed at 3 to 4 weeks postoperatively, presumably from degradation and sloughing of the stent - transient effect.

Permanent Stents

- UroLume
- Memotherm
- Permanent stents were initially introduced as treatment for recurrent urethral strictures and were subsequently used in patients with lower urinary tract symptoms (LUTS)
    1. Detrusor - Sphincter Dyssynergia
    2. Post brachytherapy BOO
    3. Anastomotic strictures and urinary incontinence after
    4. Radical prostatectomy
    5. Complex urethral strictures

3. TUNA

- Uses low-level radiofrequency (RF) energy that is delivered by needles into the prostate and produces localized necrotic lesions in the hyperplastic tissue. Delivered under topical anesthesia to patients with symptomatic BPH, causing very precise and reproducible lesions within the prostate. The TUNA consists of a special catheter attached to a generator.
- At the end of the catheter are two adjustable needles that are withdrawn into two adjustable shields made from Teflon. The needles are advanced into the prostatic tissue and can be placed accurately into the required position.
- The generator produces a monopolar RF signal of 490 kHz, temperature 100 c which allows excellent penetration and uniform tissue distribution. The patient has a grounding pad placed over the sacrum, and the current passes toward this through the prostatic tissue. The active electrode has a small surface area, with the RF current being concentrated in an area immediately surrounding it.
- TUNA system can create 1-cm necrotic lesions without difficulty in the prostate with no damage to rectum, bladder base, or distal prostatic urethra.
- The effect of TUNA was to halve the mean IPSS at 1 year. The PFR increased by about 70% from baseline to 1 year. 14% requirement for reoperation because of lack of efficacy of the primary treatment with TUNA - it occurred in less than 2 years.

4.TUMT-

MOA-

- Heat changes and differential blood flow in the prostate
- Damage to the sympathetic nerve endings
- Induction of apoptosis.

Tissue exposed to a minimum of 45° C for about 60 minutes suffered hemorrhagic necrosis with uniform extirpation of tissue. The border between viable and necrotic tissue was sharply defined .As heat energy was delivered, the blood flow rose in a marked and sustained manner.

At 6 months, the IPSS had improved from 20.0 to 9.3 and the PFR improved from 9.5 to 14.6 mL/sec. The Pdet at PFR decreased from 58.7 cm H_2O at baseline to 46.9 cm H_2O at 6 months. The mean duration of catheterization after treatment was 17.9 days, with a range of 6 to 62 days. At 3 months all treatment related complications had disappeared.

?UroLift to be included?

7. Desmopressin in BPE-

The endogenous hormone vasopressin (also known as antidiuretic hormone) has two main functions:

- Causes contraction of vascular smooth muscle
- stimulates water reabsorption in the renal medulla.

These functions are mediated by two specific vasopressin receptors, of which there are two major subtypes, namely the V1 and V2 receptors. The V2 subtype is particularly important for the antidiuretic effects of vasopressin.

- In elderly, BPH is considered the most common cause of nocturia, that is, not only inconvenient but can also have a marked effect on sleep patterns and decreases the QoL. Different treatment modalities for LUTS/BPH have been used with success.
- Nocturia does not completely respond to BPH medical treatment and alleviation of bladder outlet obstruction is not enough to overcome nocturia.
- Decreased vasopressin levels are believed to be important in the pathophysiology of some forms of polyuria, specifically NP, which can lead to symptoms such as nocturia.
- Desmopressin is the most common vasopressin analogue usednto treat nocturia. Desmopressin shows selectivity for antidiureticnover vasopressor effects.
- In giving low-dose oral desmopressin in patients with BPH and nocturia associated with NP, it was found that desmopressin resulted in a significant decrease in nocturnal voiding frequency and the volume of nocturnal urine.
- Desmopressin was well tolerated in all the studies and resulted in significant improvements compared with placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL.
- However, one of the main clinically important side effects of desmopressin use is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-hour urine volume

1. Active surveillance vs radical prostatectomy

The treatment of choice in localized carcinoma prostate in a patient with >15 years life expectancy was not defined. RP, RT and active surveillance could be used, each with its advantages and disadvantages.

ProtecT was a RCT that added information to this aspect of treatment

Methodology

- RCT that included men with localized (upto T2N0M0) CaP.
- Randomized to one of three arms: Active surveillance (545), RP (553) or RT (545).
- Longitudinal follow-up over a 10 yr period.

Endpoints

- Primary : Cancer specific mortality at 10 yrs
- Secondary:
  - All cause mortality
  - Primary treatment failure (*PSA >0.2, 3 m post RP or >2 above nadir post RT*)
  - Metastatic disease (*Bony, visceral, or lymph-node on imaging or PSA >100 ng/ml*)
  - Progression (*Mets, cT3/4, retention, long term ADT, rectal fistulae, ureteric obstruction*)

Demography

- Mean age 62 years, 99% Caucasian
- Median PSA 4.8 ng/ml
- Gleason: <7 in 77%, 7 in 20%, >7 in 3%
- Stage T1c 75% and T2a in 25%
- 80-85% received allotted treatment, 1% loss to f/u

Results

- CSS 98% in all three groups
- PFS better in treatment arm (91%) vs AS (78%)
- Twofold higher metastasis in AS group
- Similar all cause mortality
- NNT was 27 (RP)/ 33 (RT) to avoid one pt with metastasis

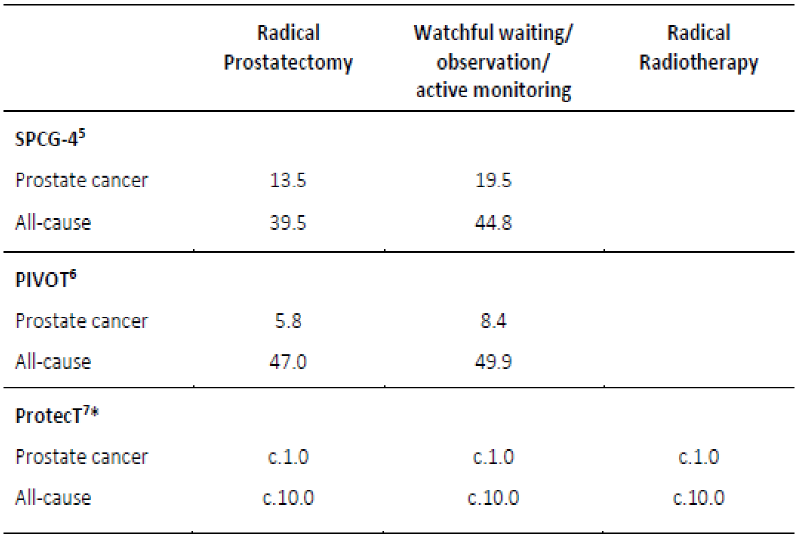
Conclusion

- In low risk Caucasian males, the three modalities provided comparable survival
- Progression and metastasis rate was higher. Treatment rate was 50% at 10 yrs in AS
- First RCT and first study to show comparable outcomes (AS survival lower in SPCG 4, PIVOT)

Critique

- Less than 1% Afro-Carribean patient population
- Recruited population may be healthier than CaP in the general population (50-69 yrs, T1c, PSA<20, Gleason 6).
- PSA based recruitment causing over-representation of low risk cancer.
- Not all patients in a group adhered to the prescribed treatment.
- The trial was conducted over two decades- diagnostic and therapeutic algorithms evolved (E.g. lap and robotic prostatectomy, IMRT).
- Longer follow-up (15 yrs) may delineate differences in survival.

Other studies (Mortality %)



	Radical Prostatectomy	Watchful waiting/ observation/ active monitoring	Radical Radiotherapy
SPCG-4[5]			
Prostate cancer	13.5	19.5	
All-cause	39.5	44.8	
PIVOT[6]			
Prostate cancer	5.8	8.4	
All-cause	47.0	49.9	
ProtecT[7]*			
Prostate cancer	c.1.0	c.1.0	c.1.0
All-cause	c.10.0	c.10.0	c.10.0

18 year follow up update of SPCG 4 (2014)- Death and metastases were reduce by 12% after RP compared to watchful waiting. (Scandinavian Prostate Cancer Group trial number 4, Prostate cancer Intervention Versus ObservaTion trial)

Patients may be counselled that survival is similar between AS and RP at the cost of higher metastasis in AS and an intervention rate of 50% at 10 years. Prostatectomy produces higher incontinence (17% vs 8% at 6 years) and ED (83% vs 70% at 6 years)

2. Saturation biopsy of prostate

For a patient with an initial negative biopsy and an elevated PSA/ abnormal DRE

Yield of repeat TRUS biopsy: 10, 5 and 4% (2nd, 3rd and 4th time).

Yield of aggressive histology: 45%, 25%, 20% (1st, 2nd and 3rd biopsies)

Defined as >12 cores. Usually more than 20 cores

Protocols vary: Six cores each: Mid peripheral, lateral peripheral and central zone. Additional cores from anterior zone

Usually trans-perineal, may be TRUS guided as well

More reproducible if a 3D template grid is used like brachytherapy

Advantages:

- More longitudinal cores from peripheral zone
- Better sampling of apex and anterior zone
- Better cancer detection (10-50% more than TRUS guided in various series)
- Better accuracy of classification
- Fewer infections (especially in diabetics)

Disadvantages:

- Increased cost due to theatre and anaesthesia
- Urinary retention in 5%
- Up to 40% cancers may be missed
- 40% Gleason scores overestimated

3. Chemoprevention of prostate cancer

Goal of chemoprevention: Reduce incidence, mortality and treatment related side effects.

Primary: Healthy individuals to prevent CaP

Secondary: Individuals with premalignant lesions (HGPIN)

Tertiary: Prevent progression of CaP

Premalignant lesions appear 20-30 years prior offering an opportunity for chemoprevention

Effective primary prevention would spare many men the burden of diagnosis and treatment

Prostate Cancer Prevention Trial (PCPT)

18882 men, >55 years, normal DRE, PSA <3 ng/ml: Finasteride 5 mg OD vs placebo for 7 years

The basis of this was absence of CaP in congenital deficiency of 5 alpha reductase

Biopsy at end of study or if clinically indicated

Results

There was a 25% reduction in prevalence of CaP with Finasteride (18% vs 24%) in 7 years

But there was an increase of Gleason 7-10 CaP with Finasteride by 15% (37 vs 22%)

The increase in high grade cancers was attributed to higher sensitivity for CaP detection after decrease in size of prostate (28% reduction with Finasteride).

Although there was an increase in high grade cancers, they were found to be more favourable (bilaterality 23 vs 31%, PNI 14 vs 20%)

Rate of insignificant cancers as per Epstein criteria was similar in both arms (36%)

No difference in overall survival

Adjustments made for higher detection rates: 30% risk reduction, non-significant 14% increased high grade cancer

Finasteride reduced AUR, need for surgery and prostatitis while it produced ED

Reduction by Dutasteride of Prostate Cancer Events (REDUCE)

Dutasteride RCT: 8231 men, 50-75 yrs, PSA 2.5-10 ng/ml, negative biopsy, prostate volume 80 cc/ lower

Reduction in risk of CaP by 23% in 4 years

Lower rate of HGPIN (1% less)

No difference in high grade cancer detection rate

Reduced AUR, need for surgery and prostatitis in Dutasteride arm

Summary

25% risk reduction with better LUTS

PCPT showed a 15% increased rate of high grade CaP. Cumulative relative risk was 1.7 (FDA)

For every 150-200 men treated, one additional man will have high grade CaP: Not safe

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Selenium showed 65% lower CaP in a trial studying its efficacy in non melanoma skin cancer

Vitamin E showed 32% lower CaP in a lung cancer prevention trial (ATBC)

35533 men studied. Four arms: Selenium+placebo, Vit E + placebo, Selenium+vit E and Placebo+placebo

>55 yrs, negative DRE, PSA <4 ng/ml. 7 yr follow-up

Hazard ratios: 1.17 (Vit E), 1.04 (Selenium), 1.05 (Combination)

So Vit E actually increased risk

Other negative trials

SWOG 9917*:* Selenium and placebo in HGPIN

National Cancer Institute of Canada*:* Soy, Vit E, Selenium and Placebo

No association: Toremefine (Estrogen receptor modulator), Statin, Metformin, Lycopene, Soy

Insufficient information: Catechins (Green tea). Reduce growth and induce CaP apoptosis in-vitro

RCT: 60 men with HGPIN. Lower CaP rate with green tea, more trials needed

4. Bone health in CaP

Introduction

- Prevalence of Vitamin D deficiency is 70% and osteoporosis is 20% in elderly men in South India.
- Hip fracture secondary to osteoporosis can result in 25% mortality at 1 year.
- With androgen deprivation, the prevalence of osteoporosis increases to as high as 80% at 10 years.
- The number needed to harm (Fracture) was 28 with LHRH agonists and 16 for orchidectomy.

Risk factors for skeletal related event

One of the following:

- >6 months on ADT,
- Previous fractures,
- Positive family history for osteoporosis,
- Low bodyweight,
- Smoking, excessive alcohol consumption,
- Corticosteroid use,
- Medical comorbidities
- Low vitamin D levels.

Baseline assessment

- Bone mineral profile (Ca^+, Phosphate, Albumin, 25(OH) Vitamin D, Alp, creatinine)
- X -RAY spine lateral (To identify sclerotic metastases that can falsely increase T score)
- Bone turnover markers: NTX (Urine N Telopeptide- resorption) and P1NP (formation)
- DXA SCAN for BMD. (T score: Patient's femur neck BMD vs. healthy young control, same gender)

BMD	T-Score
Osteoporosis	≤ minus 2.5
Osteopenia	Between minus 1.0 – minus 2.5
Normal	> minus 1.0

Lifestyle modification

Safe weight-bearing, exercise, moderate sun exposure, discourage alcohol and smoking and a balanced diet including calcium-rich foods

Calcium supplementation

- Daily requirement: 1000 mg per day
- Diet < 400 mg/ day obtained
- At least one tablet Calcium carbonate (500 mg) needed daily
- Given with dinner as acid is needed for $CaCO_3$ absorption
- Calcium citrate malate- Costly, but no acid is needed for absorption
- No Increased risk of renal stones in majority with calcium supplementation

Vitamin D

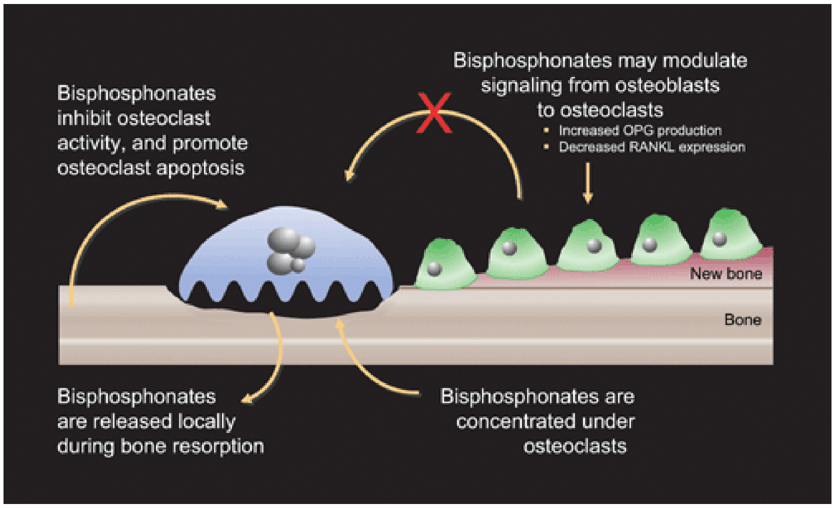
- Daily requirement: 800 U/ day
- Optimum serum 25(OH)D level for patients with osteoporosis and adults >50 yrs is 30 ng/dL
- Vitamin D deficiency: 60,000 U oral weekly for 6 weeks and monthly for 6 months.

Bone protective agents

- Treatment with bisphosphonates showed a substantial effect in preventing fractures (RR 0.80; P = 0.005) and osteoporosis (RR, 0.39; P <0.00001) and should be recommended in mCaP.
- Always prescribe calcium and Vitamin D supplementation along with these agents

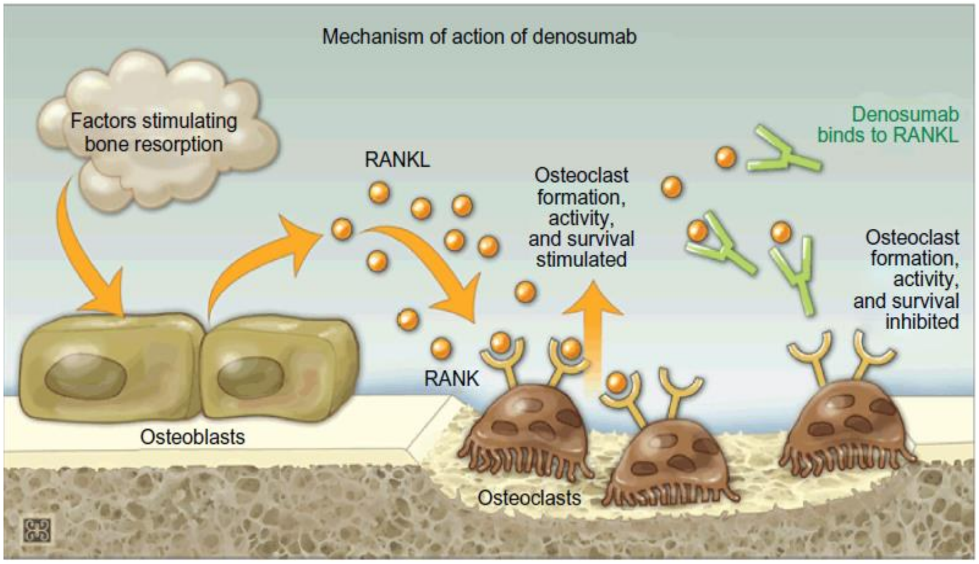
Zoledronic acid

- Nitrogen containing Bisphosphonate that acts by inhibiting the enzyme Farnesyl pyrophosphate synthase (FPP) which is required for prenylation of proteins.
- This produces cytoskeletal abnormalities in osteoclasts and detachment from bone
- It binds to the hydroxyapatite sites on the bone and when this is taken up by osteoclasts, the formation of ruffled border is hampered
- It also hampers osteoclast progenitor development and promotes osteoclast apoptosis
- Zoledronic acid showed the best NNT, compared with placebo, in relation to osteoporosis and fracture prevention (NNT = 2.68 and 14.9 respectively). (*Neto et al. Prostate Cancer Prostate Dis. 2012*). It also increased time to first fracture.
- 4 mg IV along with ADT every month in 500 ml NS over 30 minutes
- 70 percent of the absorbed bisphosphonate is cleared by the kidney, and the remaining 30 percent is taken up by bone. Therefore, normal renal function is required for Zoledronate.
- Cost in CMC: 2200-3000 per dose
- ADR: Myalgia, fever, mild increase in creatinine, osteonecrosis of the jaw (ONJ) in those with poor dentition
- Other bisphosphonates: Pamidronate, Ibadronate, Etidronate


Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis
Bisphosphonates may modulate signaling from osteoblasts to osteoclasts
• Increased OPG production
• Decreased RANKL expression
New bone
Bone
Bisphosphonates are released locally during bone resorption
Bisphosphonates are concentrated under osteoclasts

Denosumab

- Fully human monoclonal antibody against RANK ligand
- Denosumab (*Xgeva)* acts by inhibition of RANKL (also known as NF-kB) which inhibits osteoclast activity
- 60-120 mg monthly, subcutaneous
- Does not require renal dose adjustment
- Compared with Zoledronate in a phase III RCT, it showed lower skeletal resorption (lower NTX and ALP) as well as increased time to skeletal related event (20.7 vs. 17.1 months, HR 0.82, p=0.008).
- Cost in CMC: 26000 per dose
- ADR: Fatigue, nausea, hypocalcaemia, hypophosphataemia, ONJ (2-4%)


Mechanism of action of denosumab
Factors stimulating bone resorption
RANKL
Osteoclast formation, activity, and survival stimulated
Denosumab binds to RANKL
Osteoclast formation, activity, and survival inhibited
RANK
Osteoblasts
Osteoclasts

5. PSA bounce

A **temporary increase in PSA after EBRT/ BT** (external beam RT or brachytherapy) that spontaneously **decreases without intervention to a baseline** level equal to or less than prebounce PSA

Since most labs show a standard deviation of 1 ng/ml for PSA, the bounce should be >/= 2 SD or **>2ng/ml above nadir after RT** (**Most accepted definition)**.

Varying definitions: >/= 0.1, 0.2, 0.4 ng/ml (in 6 months), 0.5

>15%, >20% of most recent value, >35% of prebounce value

First described in 1997 by Wallner

Duration after treatment for bounce	**12-30 months** (Median 18)
% of patients in whom it is seen	**30-40%**
Lasts for	**6-16 months**
Magnitude of PSA increase	**0.4-1 ng/ml**
Significance of bounce	**Lower biochemical failure** (? More tumour necrosis)
Bounce vs biochemical failure	**18 months** (bounce) **vs 30 months** (failure)

Differential diagnosis: Lab error, biochemical recurrence, UTI, sexual activity

Etiology:

- -Cell **membrane instability**
- -**Infarction** and necrosis due to microvascular occlusion after RT
- -**Prostatitis**
- -**Lab error**

Predictive factors

Risk factor	Higher bounce if…	Explanation
Age	<60 yrs (2X)	Sexual activity, delayed apoptosis, reactive epithelium due to higher androgen levels
Stage	T2>T1	More tumour
Prostate/ transitional zone volume	High volume	More tissue
Radio-isotope	I^{125} vs Pd^{103} (2-3X)	Longer half life of I^{125}- slower kill
Prior ADT	ADT naïve	Testosterone induced recovery
Pre-treatment and nadir PSA	Higher PSA (Nadir >0.2)	More tissue
PSA velocity before treatment	Lower	Unknown
EBRT dose	Lower	Less necrosis and more residual tissue
BT dose	>160 Gy	More inflammation

6. Embryology and anatomy of the prostate

Embrology

Wolffian duct: 4 weeks. Vas, seminal vesicles, ureters

Mullerian duct: 6 weeks, tube formed between gonadal and mesonephric parts of urogenital ridge

Urorectal septum separates urogenital sinus from anorectal canal at 6 weeks

Germ cells reach mesenchyme at 6 weeks.

Under SRY influence, Sertoli cells and germ cells form testes cords by 7 weeks

Germ cells develop lumen and form thin walled rete testes ducts which connect to ductuli efferentes

As Sertoli cells develop, they secrete MIS (Mullerian Inhibiting Substance, a glycoprotein)- Mullerian duct regression between 8-10 weeks

Leydig cells form from mesenchyme in response to SRY and produce testosterone between 8-12 weeks

Wolffian duct develops into epididymis and vas. Epididymis makes contact with ductuli efferentes at 9 weeks

5 paired cords of cells grow from urogenital sinus epithelium into surrounding mesenchyme 10-12 weeks under the influence of DHT derived from testosterone

Interaction with mesenchymal stroma is vital for differentiation of prostatic epithelium from urothelium of the urogenital sinus. Mesenchymal stromal androgen receptors are needed for this process.

Solid cords canalize from urethra outwards and form luminal and basal cell types. Mesenchyme forms smooth muscle and connective tissue surrounding these glands and directs formation of lobes

Upper ducts form the transitional and lower ducts the peripheral zones. PZ has higher mitotic rate

Implicated genes: Hox, FGF, Activin A, Follistatin, GH, IGF-1, SHH, Bmp4, p63

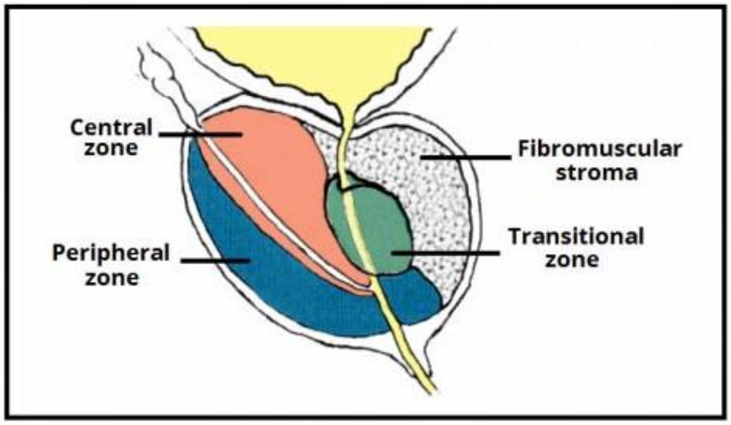
No prostate development in 5 alpha reductase deficiency

Anatomy

Zones

- Transitional: Periurethral (5%)- 20% cancer, BPH arises here
- Central : Between ejaculatory ducts and urethra (25%)- 10% cancer
- Peripheral : Posterior to central from bladder base to apex (70%)- 70% cancer
- Anterior fibromuscular stroma: Anterior to urethra (<1%)- Cancer rare

70% gland and 30% stroma. Cuboidal cells



-3X4X2 cm, 20 gm
-Homologous to glands of Skene in women
-Pyramidal, base at bladder neck and apex in contact with rhabdosphincter
-Posterior to symphysis pubis, anterior to seminal vesicles, terminal vasa and rectum. Separated by Denonvillier's fascia from the rectum.
-Anterior, posterior and two lateral surfaces
-True capsule is absent at base and apex. Continuous with outer longitudinal muscles of detrussor
-Ejaculatory ducts pass between the peripheral and central zones in an antero-inferior direction before they converge on the seminal colliculus/ veru.

-Neurovascular bundle between true capsule and endopelvic fascia at 5 and 7 O' clock

-Inferior vesical artery with capsular branches along the surface. Run caudally and turn backwards at the apex to supply the urethra and transitional zone. They are located at:

- 10 and 2 O' clock: Arteries of Flocks
- 5 and 7 O' clock : Arteries of Badenoch

-Periprostatic plexus drains to deep dorsal vein of penis, internal iliac veins and connects with the valveless intra-vertebral Batson's plexus which is the route of osseous dissemination of CaP.

-Primary nodes are Obturator and internal iliac. Smaller proportion to ext iliac and presacral

-Autonomic nerves travel along with capsular branches. Sympathetic: Capsular and stromal contraction. Parasympathetic: Secretory.

-TRUS identifies zonal anatomy. Distinct echogenic fibrous tissue separates transitional from peripheral zone. Volume: 0.625XLXWXH. Normal IPP <5 mm and normal mid-urethral angle 35 degrees

-Internal sphincter is formed by the periurethral smooth muscle (inner longitudinal + outer circumar), bladder neck and prostatic smooth muscle. Innervation is sympathetic.

-Apex is closely related to rhabdosphincter and the pelvic floor which contribute to continence after TURP.

-Endoscopically, there is a median lobe at the bladder neck, the floor (5-7 O' clock) and two lateral lobes along with anterior stroma. Resection extends from bladder neck to the veru in order to spare the rhabdosphincter.

-Nesbit sign: Pull resectoscope out of prostatic urethra and push gently forwards. The interval between the distal prostate and proximal rhabdosphincter is identified by radial mucosal crinkles.

Primary and salvage cryotherapy in CaP

Rationale

No survival benefit (PIVOT) and 5% benefit (SPCG-4) with RP vs watchful waiting at 10 years

Radical treatment: Incontinence (5-20%), impotence (30-90%), proctitis (5-20%), cost

Minimal benefit to screening in ERSPC and no benefit in PLCO

Active surveillance has showed PFS and CSS of >98% at 8 years in most studies

Difficulty in identifying clinical significant prostate cancer- Overtreatment affects QoL

TRUS biopsy: Overestimates insignificant cancer (17-19%)

Misses 30-45% of cancers (Apex, anterior, paraurethral/ transitional zone)

Does not always sample the full length of the tumour- Misclassifies grade/ volume (50%)

Unreliable if repeated + poor yield: 20%, 15%, 10% and 5% (1st, 2nd, 3rd, 4th rpt biopsy)

Haematuria (15%), haematospermia (40%), UTI (1-8%), sepsis (1-4%), AUR (0.5%)

The largest/ highest grade lesion often leads to progression though CaP is multifocal (2-3 foci/ patient)

As index lesion increases in size, it suppresses the growth of other tumour loci by paracrine effects

Evaluation of metastatic lesions observed most of them to be monoclonal, i.e. from one lesion

Treatment of most significant lesion preserves function and controls cancer effectively

Definition of clinically significant CaP

>0.5 ml, >3 mm lenth, >/=3+4 Gleason,

Indications

- Localized, non-metastatic low or intermediate risk CaP with clinically significant cancer
- 40 cc or smaller gland, no prior TURP, >10 yr expected survival (curative intent)
- Focal ablation: Up to Gleason 3+4, PSA 10 ng/ml, cT2aN0M0, PSA velocity >2 ng/ml/yr

Mechanism of action

- Freezing- Ice crystals within cytoplasm and organelles damages membranes
- Intercellular ice draws water out of cells and dehydrates them
- Endothelial injury causes thrombosis and ischaemia
- Thawing increases extracellular water and permeability causing cellular oedema by osmosis
- Reperfusion injury by oxidative free radicals
- Immunostimulation
- Coagulative necrosis at the centre and apoptosis at the periphery of ice ball

Technique

Pre-op imaging- TRUS, mpMRI. Saturation biopsies may improve sensitivity and detect significant CaP

Extended lithotomy, GA (preferred). Enema night before and morning, prophylactic Fluoroquinolone/ Ampi+Genta

18 F Foley's with 60 ml saline in balloon

TRUS/ MRI TRUS fusion to plan. Inject saline into Denonvilliers to displace rectum

4 probes- 2 anterior and 2 posterior, thermocouples: Denonvilliers, prostatic apex, NVBs

Probes should be 0.5 cm from rectum/ urethra, 1 cm from capsule and 2 cm from each other

Perineal placement of probes/ thermocouples using brachytherapy template used

Remove catheter

Cystoscopy to check if urethra safe followed by warming catheter for continuous warm saline (40 C)

Glands larger than 40 cc- 6 probes

Systems: Cryocare CS/ Visual-ICE, Argon for freezing and Helium/ passive thawing

Ice ball of 6X4 cm, 59 cc volume generated with core temperature of -40 C under real time TRUS

Peripheral temperatures at the thermocouples should be limited to 15 C

Double freeze thaw cycle followed by rectal examination to confirm that there are no ice crystals

CBD for 5 days. Alpha blockers, antibiotics, tapering methylprednisolone

Follow up

1st 2 yrs: PSA every 3 months, 3-5 yrs: Every 6 months and then annual

MRI/ biopsy if failure by Phoenix/ Astro criteria.

(Since prostate is not completely ablated, PSA is never undetectable)

Predictors of favourable outcome

<4 cores, <30% volume per core, PSA nadir <0.4 ng/ml

Outcomes

Primary

PFS of 95, 90 and 60% at 5 yrs for low, intermediate and high risk disease (10y: 70, 60, 45%)

25% have persistently positive biopsy

Inferior results for cT3 disease (45%)

Focal

PFS of 75% at 3 years

Positive biopsy of 14%

Salvage

Post RT/ RP biochemical recurrence- Salvage RP is technically demanding with risk of bleeding, rectal injury and ED

PFS of 60% at 5 yrs and 40% at 10 yrs

More side effects noted

10 yr CSS was >95% in all

Focal salvage

PFS of 47 and 42% at 5 and 10 yrs

18% positive biopsy rate, higher complication rate

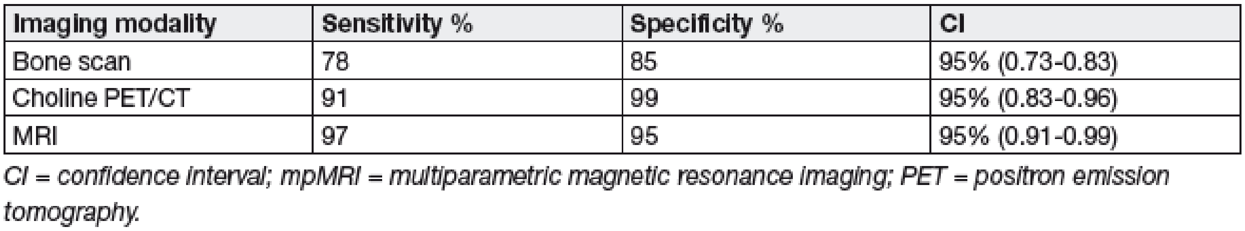
Complications

- ED (70-90%)
- Urethral sloughing (0-15%)
- Stricture (0-3%)
- Rectal fistula (0-3% with primary and 6% with salvage)
- Incontinence (3-5% with primary and 4-20% with salvage)
- Perineal pain (3% with primary, 4-20% with salvage)
- Penile oedema, perineal ecchymosis (Common)

Management of mCaP (bone disease)

Investigations

1. CBC, creatinine, LFT, PSA, urine culture, flow-PVR
2. 12 core TRUS biopsy if nodule, 2-3 cores if most of prostate involved with clinical evidence of metastases
3. Tc99 MDP bone scan
4. CT/ MRI abdomen and pelvis



Imaging modality	Sensitivity %	Specificity %	CI
Bone scan	78	85	95% (0.73-0.83)
Choline PET/CT	91	99	95% (0.83-0.96)
MRI	97	95	95% (0.91-0.99)

CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

Choline is most specific while NaF is most sensitive for bone metastases

MDP positivity: PSA-<10: 2%, 10-20: 5%, >20: 15%

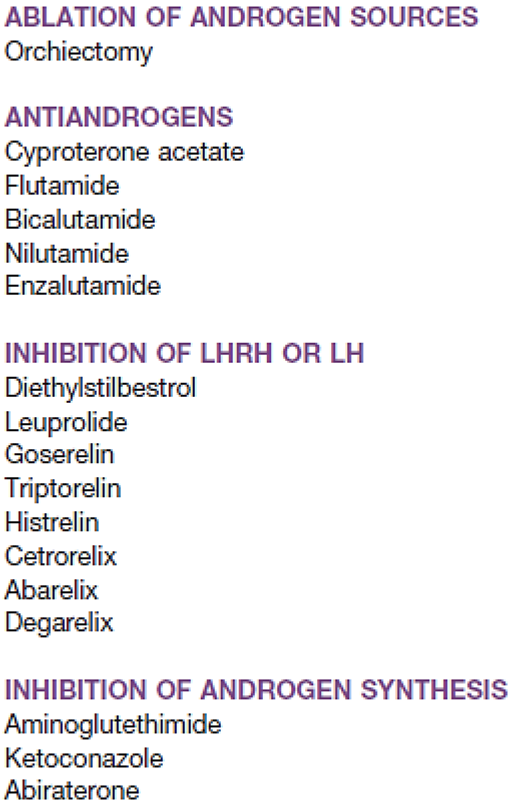
Gleason up to 7: 5%, >7: 30%

Up to cT2: 5%, >T2: 50%

Prognostic factors

- Performance status, Gleason, PSA, ALP, LDH, high vs low volume disease (>4 bone lesions, at least 1 outside spine/ pelvis or visceral metastases- high volume)
- PSA after 7 months of ADT (SWOG 9346): <0.2: 75 months, 0.2-4: 44 months, >4: 13 months median OS
- Overall median survival in newly diagnosed mCaP is 42 months

***ADT* (**First line therapy)



ABLATION OF ANDROGEN SOURCES
Orchiectomy

ANTIANDROGENS
Cyproterone acetate
Flutamide
Bicalutamide
Nilutamide
Enzalutamide

INHIBITION OF LHRH OR LH
Diethylstilbestrol
Leuprolide
Goserelin
Triptorelin
Histrelin
Cetrorelix
Abarelix
Degarelix

INHIBITION OF ANDROGEN SYNTHESIS
Aminoglutethimide
Ketoconazole
Abiraterone

Bilateral orchidectomy

Orchidectomy is gold standard with >90% castrate by 12-24 hrs. Cheap, easy to perform, permanent
Subcapsular or total, useful in quick symptom relief especially in cord compression/ severe pain/ ureteral obstruction

Pharmacotherapy

	Time to castration	Mechanism of action	T1/2	Dose	Adverse effects	Special characteristics
Cyproterone acetate	-	-Steroidal antiandrogen. ---Central progestational (low testosterone)		100 mg TID	Fluid retention, cardiovascular, gynaecomastia (20%), Hepatitis	Useful in treatment of hot flushes.
Flutamide	-	-Non-steroidal antiandrogen (NSAA) -Central and peripheral AR blockade	6 hrs	250 mg TID	Diarrhoea	Renal clearance
Nilutamide	-	"	56 hrs	150 mg OD	-Delayed dark adaptation -Interstitial pneumonitis (1%) -Alcohol intolerance	Hepatic clearance
Bicalutamide	-	"	6 days	50 mg OD (CAD), 150 mg OD (monoRx)	Gynaecomastia and pain (70%)	-Not affected by renal/ hepatic dysfunction. -Libido preserved in NSAA
Leuprolide	3 wks	LHRH agonist- Receptor downregulation by persistent stimulation. Blocks FSH. LH release	Depot	22.5 mg im every 3 m, 7.5 mg im every month	Flare- Worsening bone pain, spine compression, BOO, AKI	Prevent with 50 mg OD Bicalutamide for 4 weeks simultaneous
Degarelix	96% in 3 days	LHRH antagonist	Depot	240 mg s/c stat and 80 mg per month	Injection site pain	Avoids flare esp in cord compression
Ketoconazole	4 hrs	-Blocks 14 alpha demethylase- blocks lanosterol to cholesterol conversion. -Blocks 17,20 lyase	8 hrs	400 mg TID + Hydrocortisone 20 mg BD	Gynaecomastia, weakness, nausea, hepatic dysfunction	Testosterone low normal by 5 months

Abiraterone (Inhibitor of 17 alpha hydroxylase and 17, 20 lyase) and Enzalutamide (Blocks AR as well as receptor nuclear translocation) are used in CRPC setting

All these drugs produce general complications due to androgen blockade

Common adverse effects of ADT

- Osteoporosis-100% in 4yrs, risk of fracture
- Increase in weight by 2-4%
- Diabetes/ metabolic syndrome in 50%
- Loss of libido and ED in 80%
- Hot flushes in 50-80%
- Gynaecomastia in 70%
- Anaemia in 90%
- 20% increased cardiovascular morbidity and mortality

Androgen withdrawal phenomenon

Combination therapy with antiandrogens and LHRH agonist

Probable due to AR agonist activity of antiandrogen

15-30% patients may show >50% drop in PSA when antiandrogen in stopped

PSA decline seen at 4 wks after Flutamide and 6 weeks after Nilutamide/ Bicalutamide withdrawal

Clinical response

Nadir PSA usually at 7 months after ADT initiated

Those with >80% PSA drop in 1 month, undetectable PSA do well

HR for CRPC=15 if PSA detectable and 70% higher risk for CRPC with each unit increase in Gleason

Complete Androgen Blockade <5% OS benefit at 5 yrs with risk of androgen withdrawal phenomenon

Immediate (vs delayed) ADT improved survival and lead to lower symptom progression

Intermittent ADT

Useful in men with minimal symptoms of mCaP, regular on follow-up and who would like to minimize adverse effects of ADT

After induction LHRH agonist/ antagonist for 6 months, stop injections if PSA <4 ng/ ml

Restart if symptoms progress or PSA> 10-20 ng/ml

Not inferior to continuous ADT, may delay progression to CRPC, cost effective
However, can produce microsurges of Testosterone, needs intensive 3 monthly surveillance and may compromise OS

LHRH agonist vs antagonist

Degarelix vs Leuprolide phase III RCT (Klotz et al, BJUI 2012)

Lower Testosterone at 3 days and 1 month with Degarelix. Equal at 8 weeks

No flare seen with Degarelix

Lower PSA at 1 month and 12 months with Degarelix

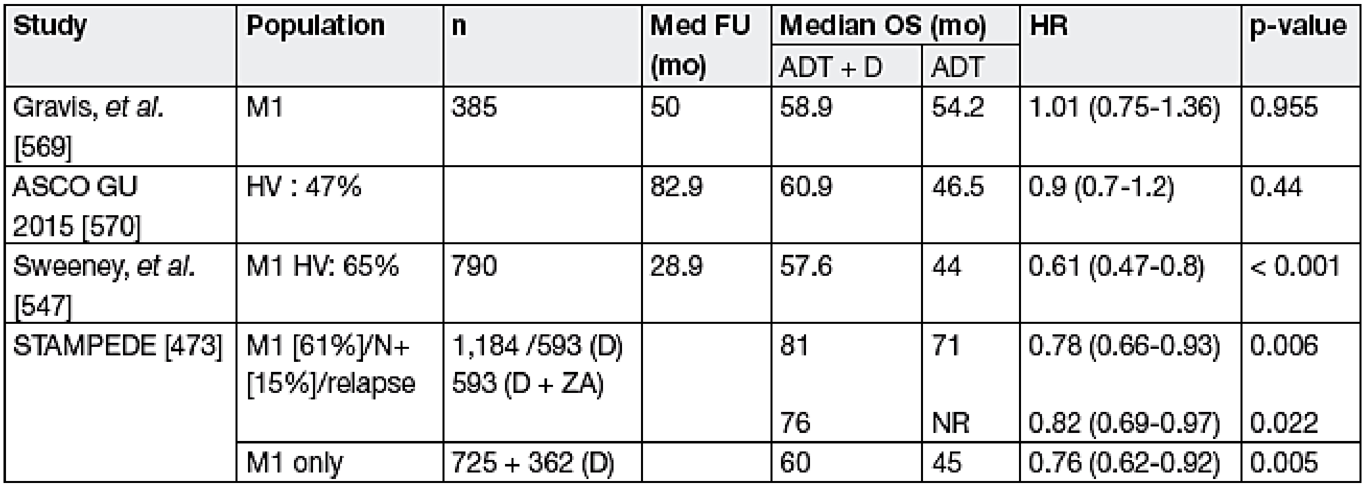
Higher PFS (5%), OS (3%) at 1 yr with Degarelix on retrospective review - Needs prospective validation

Lower cardiovascular morbidity with Degarelix (? Lower FSH)

Combination with Abiraterone

Study	Population	N	F/u median	Med OS ADT+A	Med OD ADT	HR	p
STAMPEDE	M1 (52%)/ N+/ N0M0	1917	36 m	83%	76%	0.63 (0.52-0.76)	<0.001
LATITUDE	M1	1199	30.4 m	NR	34.7 m	0.62 (0.51-0.76)	<0.001

Combination with Docetaxel



Study	**Population**	**n**	**Med FU (mo)**	**Median OS (mo)**		**HR**	**p-value**
				ADT + D	ADT		
Gravis, *et al.* [569]	M1	385	50	58.9	54.2	1.01 (0.75-1.36)	0.955
ASCO GU 2015 [570]	HV : 47%		82.9	60.9	46.5	0.9 (0.7-1.2)	0.44
Sweeney, *et al.* [547]	M1 HV: 65%	790	28.9	57.6	44	0.61 (0.47-0.8)	< 0.001
STAMPEDE [473]	M1 [61%]/N+ [15%]/relapse	1,184 /593 (D) 593 (D + ZA)		81 76	71 NR	0.78 (0.66-0.93) 0.82 (0.69-0.97)	0.006 0.022
	M1 only	725 + 362 (D)		60	45	0.76 (0.62-0.92)	0.005

Role of RP/ brachytherapy

SEER database: M1 patients-No Sx/ RT (n=7811), RP (n=245), and brachytherapy (n=129).

5-yr OS: RP (67.4%), RT (52.6), no Sx/RT (22.5%)

Retrospective, selection bias, needs prospective validation

Munich cancer registry: RP (55%), RT and ADT (25%) 5 yr OS

Clearly, further prospective RCTs are the need of the hour

Bone health

Please refer to short note in part 1

Treatment of spine compression ***refer to SCORAD notes)

Start Dexamethasone 10 mg stat and q6h

Prompt ADT: B.l orchidectomy/ Ketoconazole 400 mg TID + Hydrocortisone 20 mg BD/ Degarelix 240 mg s/c stat

Pain management according to WHO pain ladder: Paracetamol—NSAIDs—Opioids, Gabapentin

CT/ X ray spine to rule out osteolytic lesion

MRI spine to exclude epidural compression

RT/ spine consult

Spine RT: 8 Gy single dose or 30 Gy in 3 fractions

If unstable #, progression despite RT, paraparesis: Surgical fixation

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Management of locally advanced CaP

Definition

cT3-4, N0-1, M0

High risk disease. Incidence has decreased from 40-60% to 15%

Investigations

- CBC, creatinine, LFT, PSA, urine culture, flow-PVR
- 12 core TRUS biopsy if nodule, 2-3 cores if most of prostate involved with clinical evidence of metastases
- Tc99 MDP bone scan
- MRI abdomen and pelvis

Risk stratification (For LN+, ECE, SV+)

Nomograms: Partin (Stage, Gleason, PSA), MSKCC, Briganti (Secondary Gleason and % cores + also)

Roach formula: 2/3 PSA + (Gleason-6) X 10= Risk (%) of LN disease

Radical prostatectomy

RP may be offered only as a part of multimodality therapy. Non-nerve sparing

Should be operable (Not adherent to pelvic side wall or pelvic musculature)

Cancer specific survival 90% at 10 yrs and 60% at 15 yrs (vs. 70 and 60% with conservative therapy)

OS about 60% at 10 yrs, 35% at 15 yrs. Annual mortality stable after 15 yrs

No survival benefit to neoadjuvant ADT

Extended LN dissection (Ext, int iliac and obturator) mandatory as risk of LN+ is 15-40% (>5%)

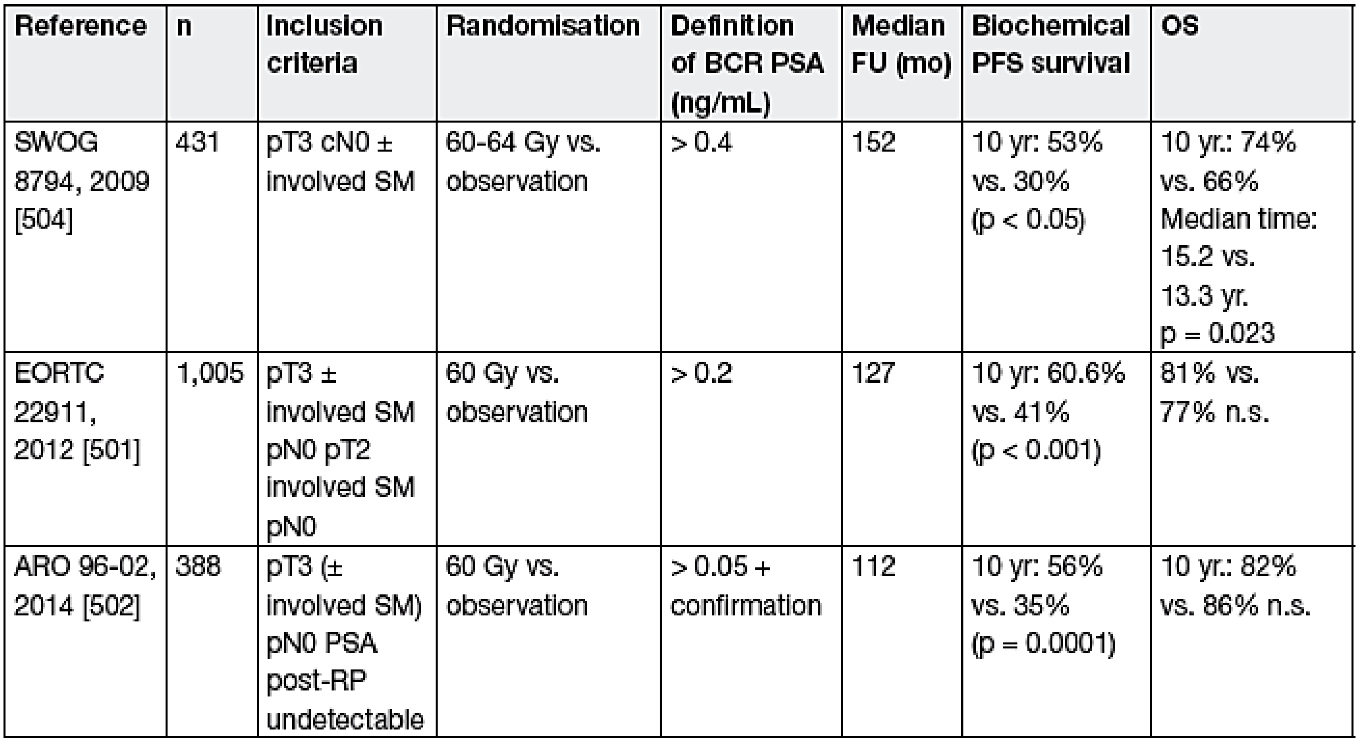
Survival was better with completion vs. abandoned lymphadenectomy in the setting of N+ disease.

Survival drops to 45% at 10 and 15 yrs if pN+

Prognosis of N+ disease depends of number of nodes harvested, density (>20% positive nodes poor prognosis), tumour volume and extracapsular spread

Adjuvant therapy after RP

- pT3/4 or positive margin- High risk of local failure (30%, 45% and 60% at 5, 10 and 15 years).
- Adjuvant RT is standard of care
- May be offered in the immediate or salvage setting if PSA <0.1 and increases to >0.5 on observation
- If PSA >0.1 ng/ml, immediate RT indicated



Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical PFS survival	OS
SWOG 8794, 2009 [504]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr: 53% vs. 30% (p < 0.05)	10 yr.: 74% vs. 66% Median time: 15.2 vs. 13.3 yr. p = 0.023
EORTC 22911, 2012 [501]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr: 60.6% vs. 41% (p < 0.001)	81% vs. 77% n.s.
ARO 96-02, 2014 [502]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr: 56% vs. 35% (p = 0.0001)	10 yr.: 82% vs. 86% n.s.

10 year PFS improved by 20% to about 60% in all 3 trials. OS benefit of 10% seen only in SWOG 8794

Adjuvant ADT improves PFS by 25% but not OS if T3/4N0

In N+ disease, OS improves from 45 to 80% with adjuvant ADT.

Definitive RT

Intensity modulated (IMRT) with image guidance (IGRT) is the present standard of care

Real time monitoring of treatment field and correction if >0.5 cm deviation

Usual dose >74 Gy. Escalation of dose to 81 Gy showed better PFS. May consider brachytherapy boost

RT showed a 55% PFS and 71% OS at 10 years with a HR of 0.82. 85% 7 yr PFS with boost

Grade 3 complications 2-5% for rectum and bladder- Higher with boost

Hypofractionation

- Smaller fractions i.e. larger dose per fraction
- Tissues with slow proliferation show repair between fractions. A larger dose per fraction produces more damage
- Increased patient convenience and lower cost
- Moderate: 2.3-4 Gy and extreme: 5-10 Gy per fraction (Normal 1.8-2 Gy per fraction)
- 5 year PFS 70-90%, higher toxicity observed. Longer follow-up needed

ADT with RT

Leuprolide/ orchidectomy. Degarelix described

Superior CSS and OS (HR 0.6-0.7)

Low risk- 3 months, intermediate- 6 months, high risk- 6-36 months (May use 150 mg OD Bicalutamide)

Usually started 3 months before RT, concomitant administration potentiates RT effects

Intermittent ADT not well studied

Cryoablation
Usually in the salvage setting. Short PFS (41% at 5 yrs)

Sequelae after RT
BOO (30%), HUN (20%), incontinence (10%), rectal obstruction (5%), proctitis, cystitis, stricture, incontinence

Chemotherapy+ADT
Investigational: Docetaxel, Estramustine + Paclitaxel + Carboplatin, Doxorubicin + Ketoconazole

Controversies in prostate cancer screening

Prostate cancer screening began in the early 90s. This lead to a stage migration wherein 81% of the newly detected cancers were localized, 75% were non-palpable and 66% were low grade

Screening is believed to have contributed 45-70% towards reduction in mortality whereas improved treatment contributed 22-33%

Prostate cancer is suited for screening because:

-It is a significant public health problem (Most common non-skin cancer, 6th commonest cause of death worldwide)

-There is a recognized pre-malignant state (HGPIN)

-There is a lead time between HGPIN and development of cancer

-It is mostly indolent (Swedish Observational Trial: 34 yr observation, 17% overall death by CaP)

-It gives ample time for intervention (Time from biochemical failure to metastasis- 8 yrs and time from metastasis to death- 5 yrs after RP- Pound et al, 1999)

-There is an economically viable, available and acceptable test for screening (PSA)

-The treatment for screen detected (i.e. localized) CaP is well established

Advantages of screening

-Detected at an earlier stage where there is a potential for cure

-Has reduced the incidence of advanced/ metastatic disease- Improved QoL

-Has reduced mortality by 20-44%

- 10 yr mortality (No active treatment):

	Pre-PSA	Post PSA
Intermediate risk	15-25%	2-5%
High risk	25-35%	50-70%

Drawbacks of screening

-Increase in insignificant cancers that may have been undetected in patient's lifetime (40%)

-Cannot identify biologically aggressive tumours- Heterogeneous biological behaviour

-Contrary results in RCTs for survival benefit

-Adds to patient's anxiety, cost and morbidity

Evidence in favour of screening

ERSPC (European Randomized Study for Screening of Prostate Cancer)

->160,000 men, 55-74 yrs, PSA<3ng/ml, normal DRE. 4 yrly screening vs usual care

-85% compliance with screening protocol with the exception of France

-13 yr follow-up

-There was a 71% increase in incidence with screening and 41% decreased incidence of incurable disease

-HR for mortality due to CaP: 0.79 (I.e. 21% less death from CaP)

-NNS: 781, NNT: 27

-Most of the advantage of screening was noted between 1-11 yrs after which, the mortality benefit reached a plateau.

-The only drawback was that the France arm's follow-up was 7 years with only 1-2 biopsies post randomization

Goteborg screening trial

-20,000 men, 50-64 yrs, 4 yrly screening till 71 yrs age vs usual care

-PSA cutoff 2.5 ng/ml (Initially 3.4 ng/ml)

-Only 3% in the control group had undergone pre-randomization screening with PSA measurement

-93% biopsy compliance, 77% complete follow-up. -1/3rd were managed with AS

-14 yr follow-up

-44% lower incidence of incurable disease and 41% lower cancer specific mortality with screening

-NNS: 208, NNT: 9

Evidence against screening

PLCO (Prostate Lung Colorectal and Ovarian) cancer screening trial

->70,000 men, 55-74 yrs, PSA<4 ng/ml (4 is a high cutoff). Annual screening for 6 yrs vs usual care

-Almost 85% contamination of the control arm with pre-randomization PSA screening

-44% prescreening in the intervention arm

-13 yr follow-up

-12% more incidence of CaP in the screening arm

-Overall mortality similar (3.4 vs 3.1/ 10,000 person years). Trial not powered for mortality

-However, subgroup analysis (Men with minimal comorbidity: 44% lower cancer specific mortality)

-NNS: 723, NNT: 5 in the men with minimal comorbidity

Drawbacks: High PSA cutoff, prescreening rates high, underpowered for mortality analysis, lack of prompt biopsy in case of high PSA in the screening arm

The US services preventive task force recommended against screening for CaP which is a flawed decision as too much weight was given to the flawed PLCO trial. Also, men at high risk (family history, Afro-American) were ignored.

It is reasonable to offer screening in light of the above mentioned evidence after discussion with a pt

EAU recommendations for screening:

->50 yrs (>45 in case of positive family history/ Afro-American descent)

-PSA >1 ng/ml at 40 yrs and >2 ng/ml at 60 yrs should be screened at 2 yrs and then at 8 yrs if negative

-F/u at 8 yrs if risk low

Familial and hereditary CaP

Familial: Clustering in a family

Hereditary: Inherited in a Mendelian fashion. Three generations, three 1st degree or two <55 yrs

43% of patients <55 yrs have hereditary prostate cancer (HPC), 15% overall CaP believed to be HPC

Earlier presentation, high grade and stage with worse survival (Esp BRCA associated)

Relative risk: Brother 3.4, father: 2.2. >two 1st degree: 5

Highest risk with BRCA2 (RR: 6.6, 30-40% lifetime) followed by BRCA 1 (RR: 2.6, 3-8% lifetime risk)

HOXB13 gene (17q), G84E mutation: RR of 4.5. Involved in prostate development

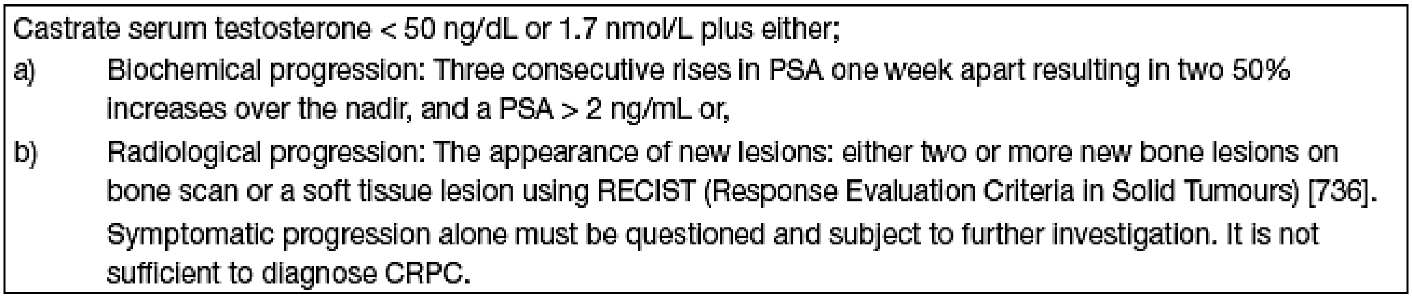
Genome Wide Association Studies (GWAS) have identified 76 loci with single nucleotide polymorphisms (SNP) including chromosomes 2,3,4,5,6,7,8,10,11,12,13,17,19,22,X

Suggestive of low penetrance of most alleles

Conflicting evidence with regard to biological behavior- 3 studies showed no difference in PFS while one showed a 20-40% lower biochemical PFS with hereditary CaP

CRPC

Table 6.10.1: Definition of Castration-resistant PCa (CRPC)



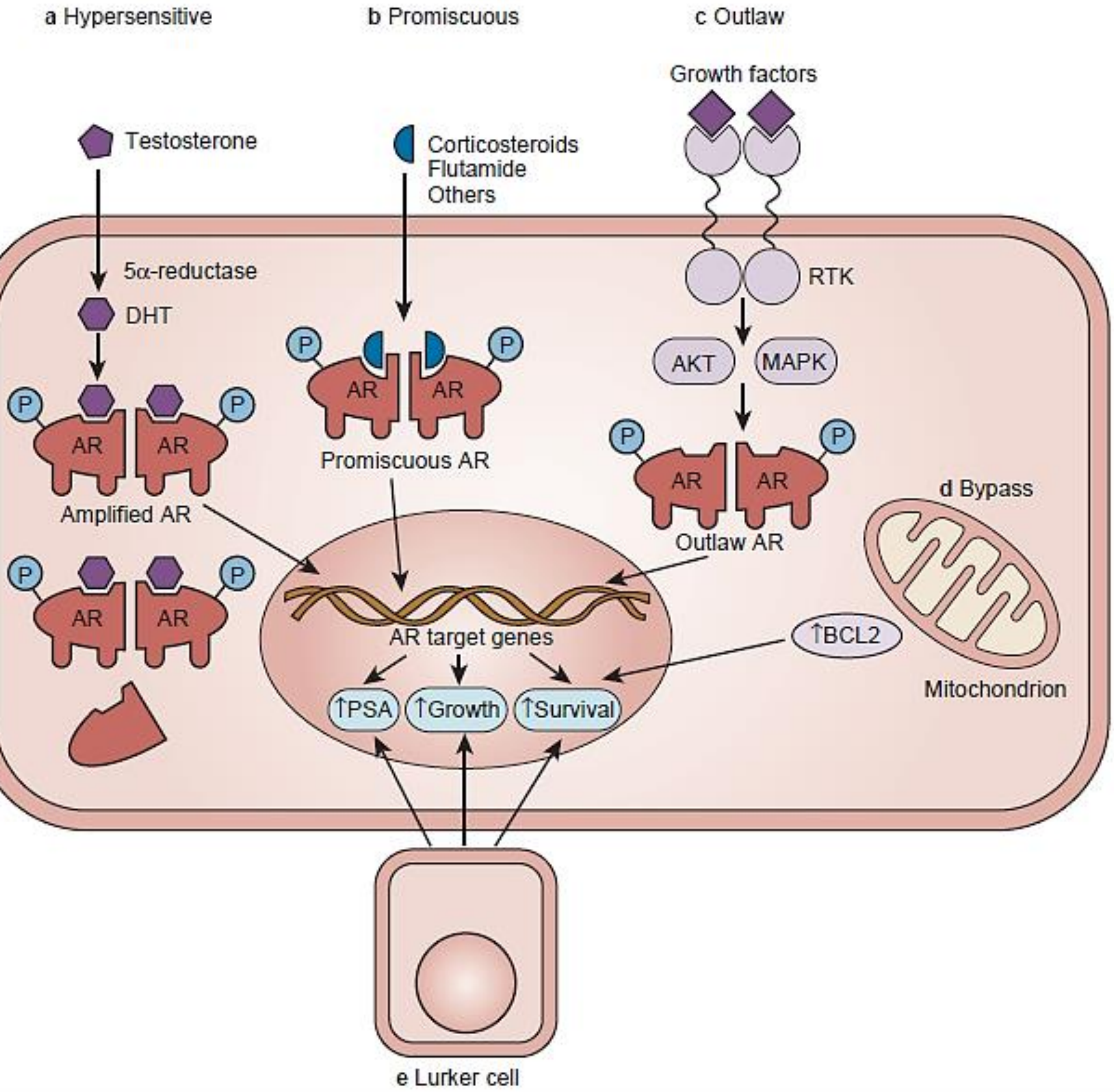
Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;

a) Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,

b) Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [736].

Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

Mechanisms of Androgen resistance



Investigations:

CBC, creatinine, LFT, PSA (3 monthly)

Bone scan and CECT thorax+abdomen when PSA reaches 2 ng/mL

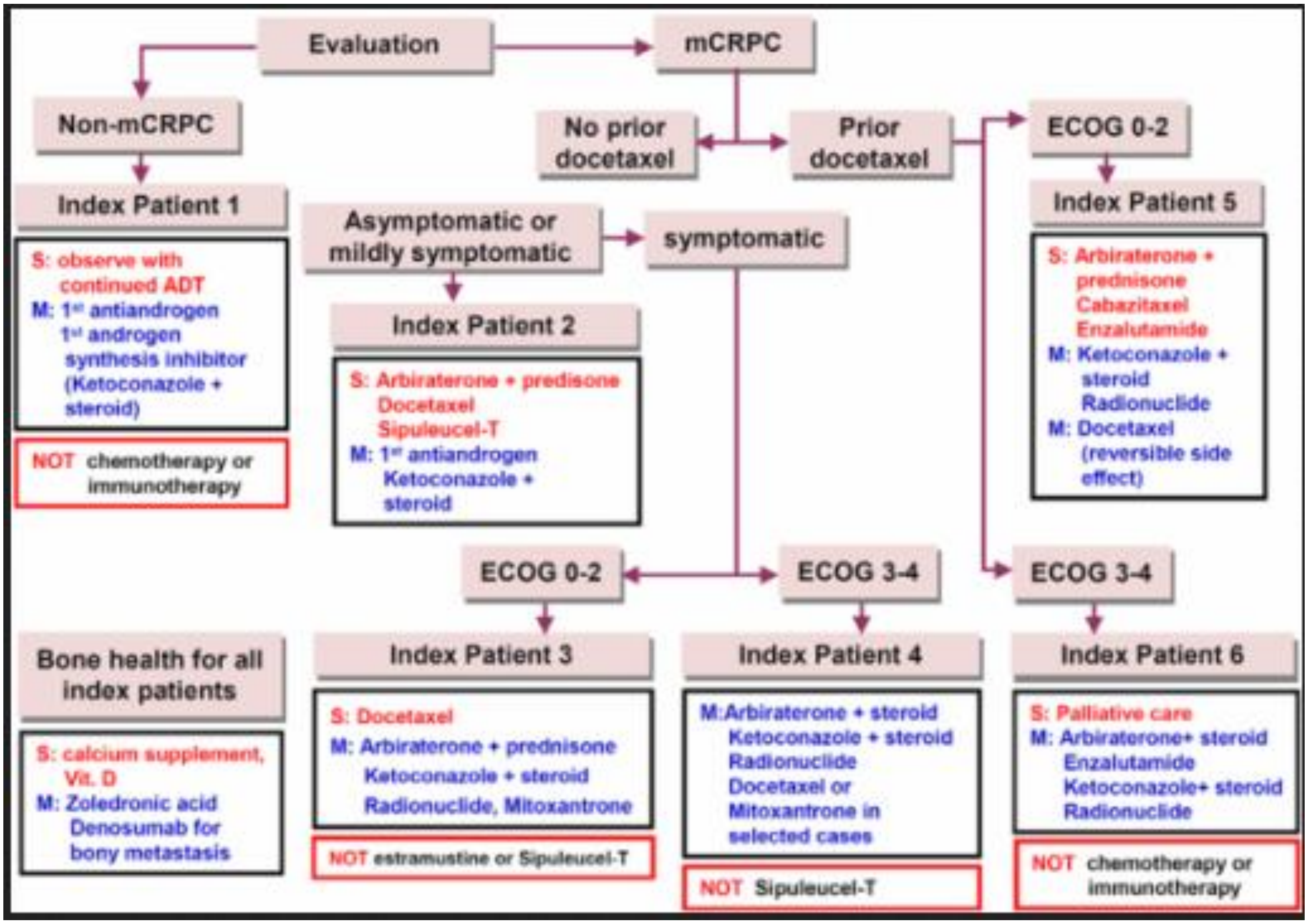
If negative it- repeat at PSA of 5 ng/ml and after every doubling of the PSA
Symptomatic patients should undergo CECT and bpne scan regardless of PSA level q6 monthly.

AUA index patients

1: Asymptomatic, non-metastatic
2: Minimally symptomatic, metastatic, no prior Docetaxel, good PFS
3: Symptomatic, metastatic, no prior Docetaxel, good PFS
4: Symptomatic, metastatic, no prior Docetaxel, poor PFS
5: Symptomatic, metastatic, prior Docetaxel, good PFS
6: Symptomatic, metastatic, prior Docetaxel, poor PFS

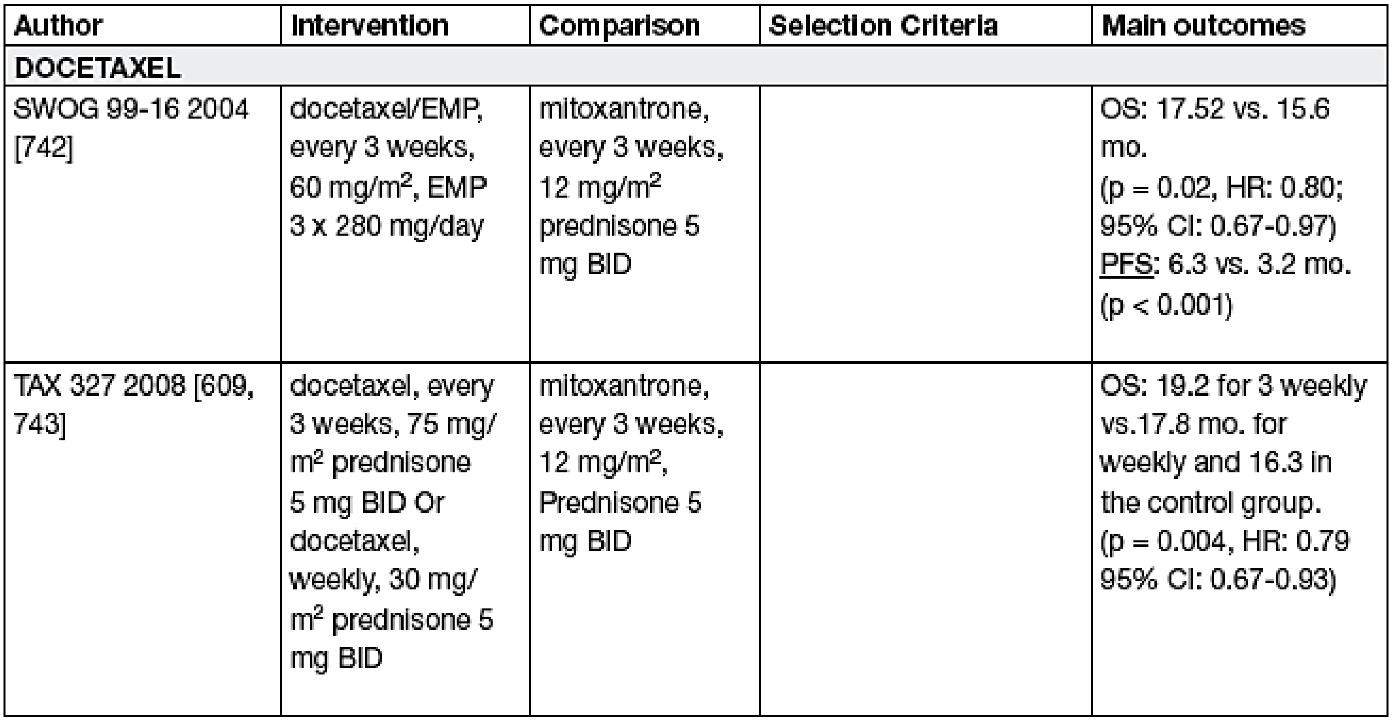
To summarize: Asymptomatic: ADT
Fit + chemonaive: Abiraterone/ Enzalutamide>Docetaxel/ Sipuleucel T/ Ketoconazole#
Fit + prior Docetaxel: Abiraterone/ Enzalutamide/ Cabazitaxel/ Ketoconazole*#
Unfit + chemonaive: Abiraterone/ Enzalutamide.*#
Unfit + prior Docetaxel: Supportive care. Optional other drugs#

*Docetaxel if poor PFS due to disease or if prior response to Docetaxel and side effects lead to discontinuation
#Ra223: Bone disease without visceral mets. PFS and prior Docetaxel doesn't matter


Evaluation
mCRPC
Non-mCRPC
No prior docetaxel
Prior docetaxel
ECOG 0-2
Index Patient 1
S: observe with continued ADT
M: 1st antiandrogen
1st androgen synthesis inhibitor (Ketoconazole + steroid)
NOT chemotherapy or immunotherapy
Asymptomatic or mildly symptomatic
symptomatic
Index Patient 2
S: Arbiraterone + predisone
Docetaxel
Sipuleucel-T
M: 1st antiandrogen
Ketoconazole + steroid
Index Patient 5
S: Arbiraterone + prednisone
Cabazitaxel
Enzalutamide
M: Ketoconazole + steroid
Radionuclide
M: Docetaxel (reversible side effect)
ECOG 0-2
ECOG 3-4
ECOG 3-4
Bone health for all index patients
S: calcium supplement, Vit. D
M: Zoledronic acid
Denosumab for bony metastasis
Index Patient 3
S: Docetaxel
M: Arbiraterone + prednisone
Ketoconazole + steroid
Radionuclide, Mitoxantrone
NOT estramustine or Sipuleucel-T
Index Patient 4
M:Arbiraterone + steroid
Ketoconazole + steroid
Radionuclide
Docetaxel or Mitoxantrone in selected cases
NOT Sipuleucel-T
Index Patient 6
S: Palliative care
M: Arbiraterone+ steroid
Enzalutamide
Ketoconazole+ steroid
Radionuclide
NOT chemotherapy or immunotherapy

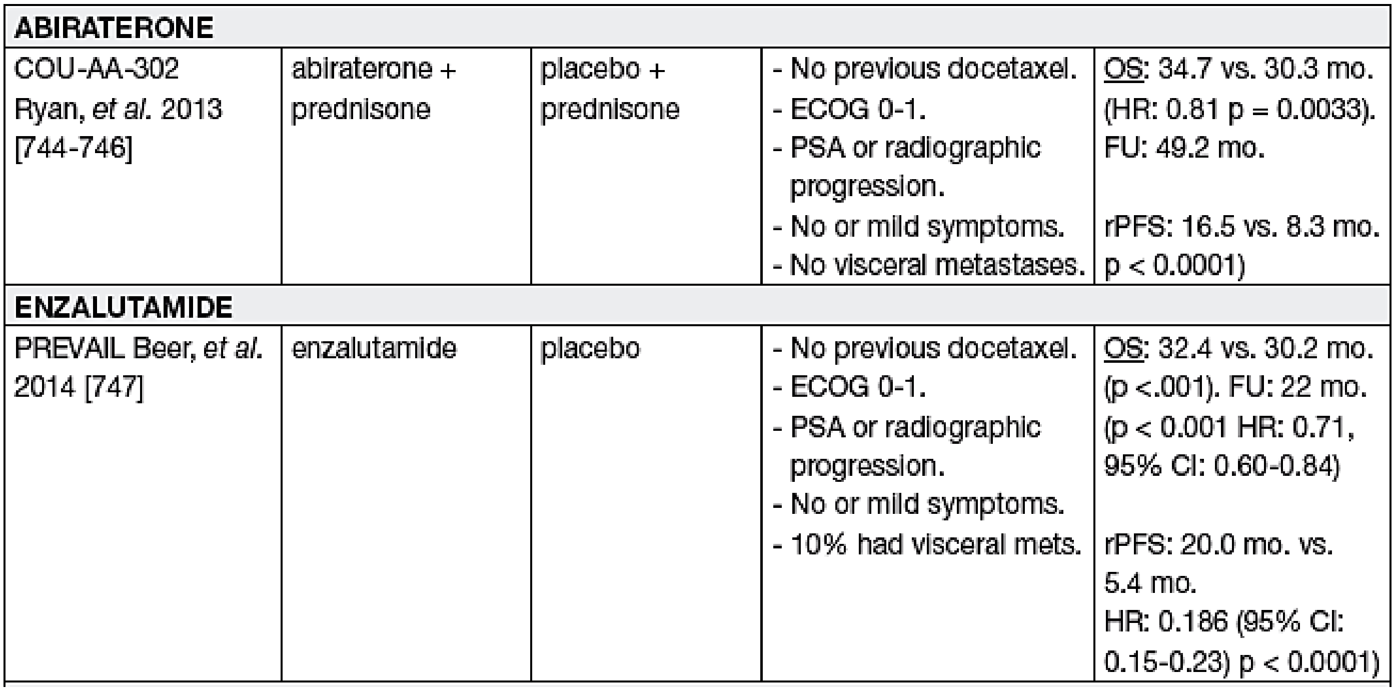
First line phase III trials

Docetaxel (75 mg/m2 IV q21 days for 10 cycles)



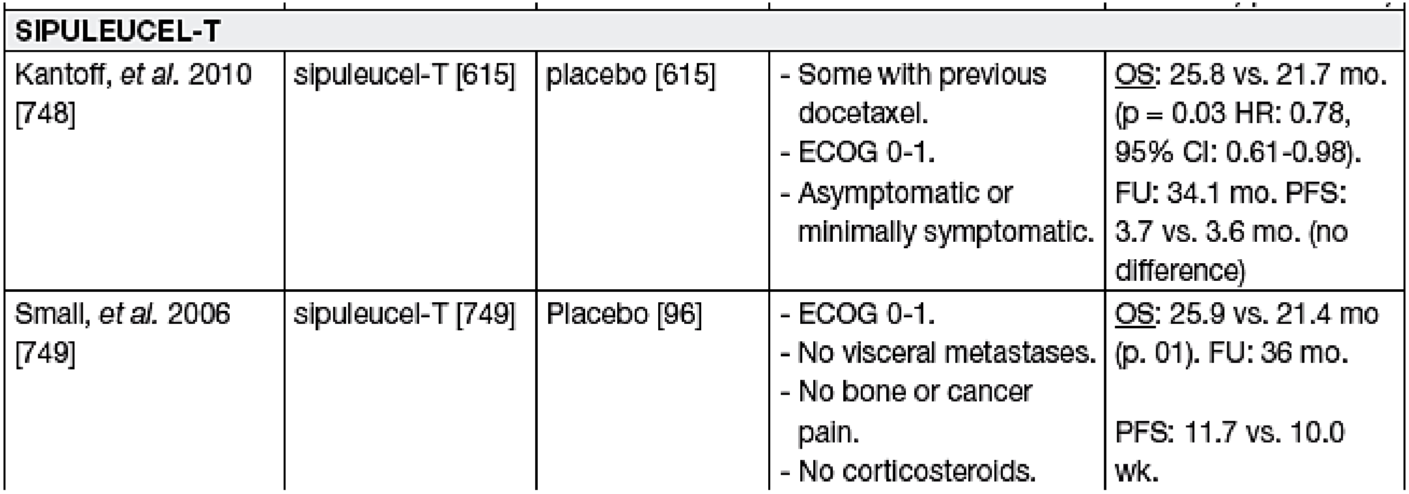
Author	Intervention	Comparison	Selection Criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [742]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) PFS: 6.3 vs. 3.2 mo. (p < 0.001)
TAX 327 2008 [609, 743]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID Or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		OS: 19.2 for 3 weekly vs.17.8 mo. for weekly and 16.3 in the control group. (p = 0.004, HR: 0.79 95% CI: 0.67-0.93)

Abiraterone (1 gm + 40 mg Prednisolone OD/ Enzalutamide (160 mg OD- both oral)



ABIRATERONE				
COU-AA-302 Ryan, *et al.* 2013 [744-746]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	OS: 34.7 vs. 30.3 mo. (HR: 0.81 p = 0.0033). FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo. p < 0.0001)
ENZALUTAMIDE				
PREVAIL Beer, *et al.* 2014 [747]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	OS: 32.4 vs. 30.2 mo. (p <.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) rPFS: 20.0 mo. vs. 5.4 mo. HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)

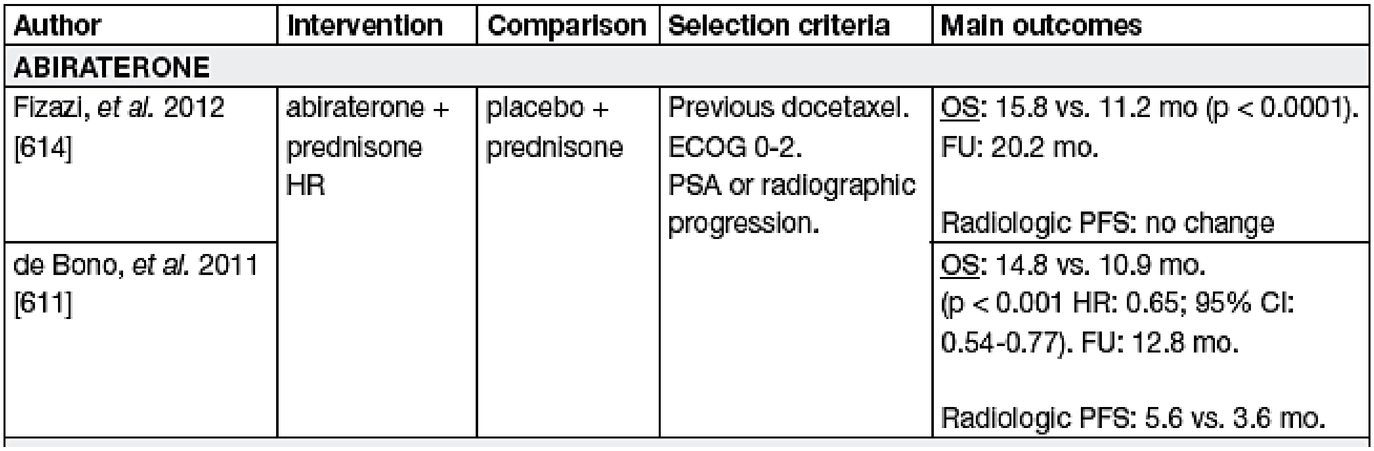
Sipuleucel T



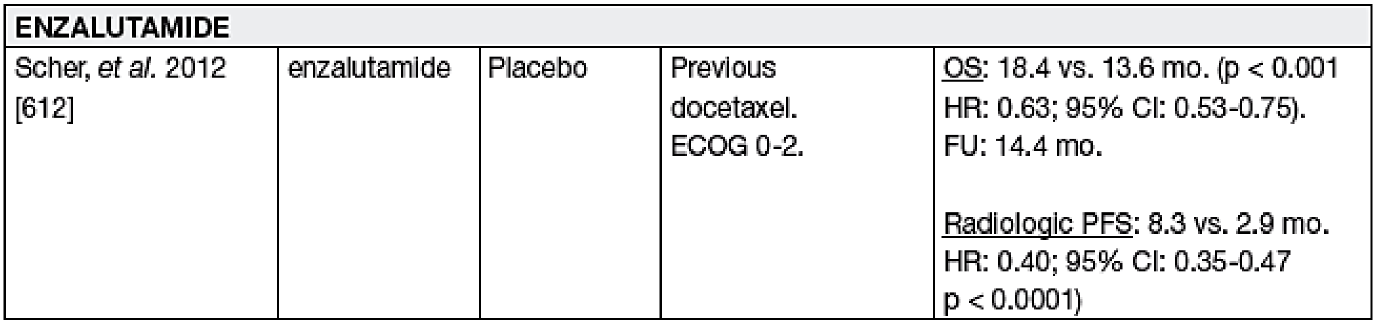
SIPULEUCEL-T				
Kantoff, *et al.* 2010 [748]	sipuleucel-T [615]	placebo [615]	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	OS: 25.8 vs. 21.7 mo. (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo. (no difference)
Small, *et al.* 2006 [749]	sipuleucel-T [749]	Placebo [96]	- ECOG 0-1. - No visceral metastases. - No bone or cancer pain. - No corticosteroids.	OS: 25.9 vs. 21.4 mo (p. 01). FU: 36 mo. PFS: 11.7 vs. 10.0 wk.

Prostvac VF: PSA targeted pox viral vaccine. Virus containing DNA plasmid with PSA+3 co-stimulatory genes. OS improvement noted 25.1 vs 16.6 months in a phase II trial

Second line trials

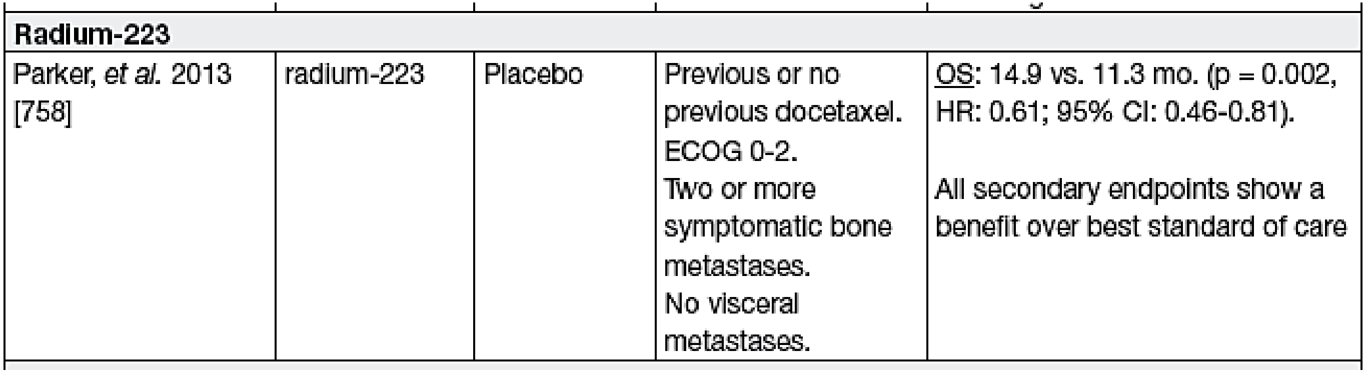


Author	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
Fizazi, *et al.* 2012 [614]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	OS: 15.8 vs. 11.2 mo (p < 0.0001). FU: 20.2 mo. Radiologic PFS: no change
de Bono, *et al.* 2011 [611]				OS: 14.8 vs. 10.9 mo. (p < 0.001 HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo. Radiologic PFS: 5.6 vs. 3.6 mo.



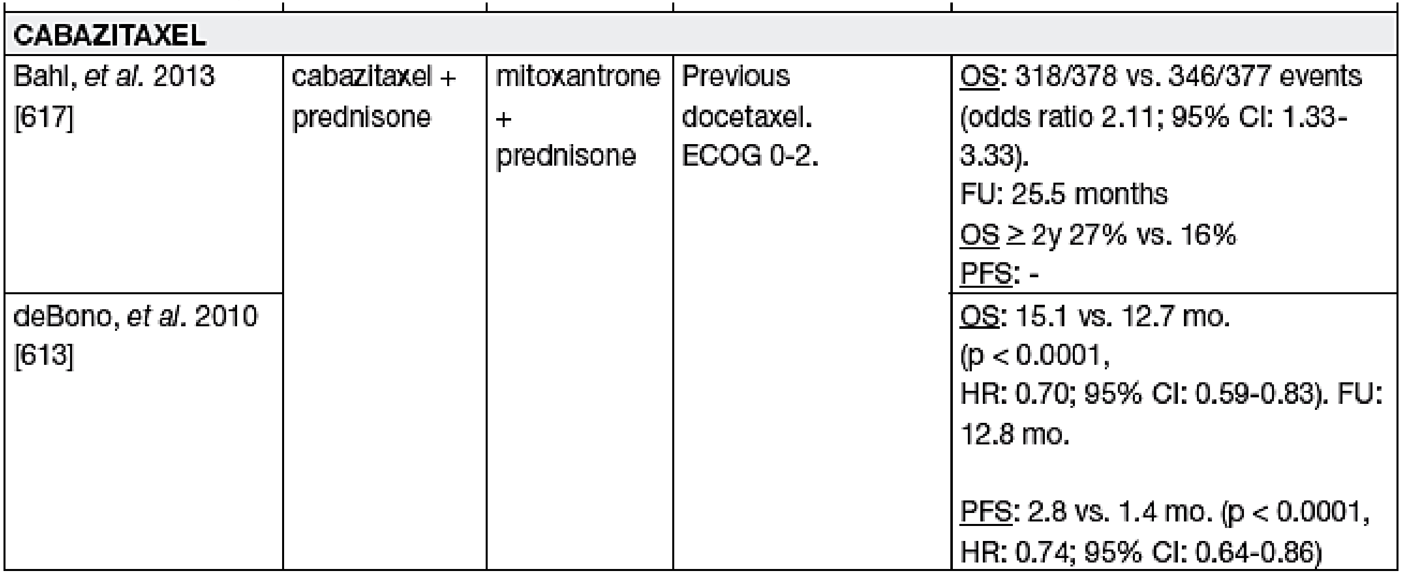
ENZALUTAMIDE				
Scher, *et al.* 2012 [612]	enzalutamide	Placebo	Previous docetaxel. ECOG 0-2.	OS: 18.4 vs. 13.6 mo. (p < 0.001 HR: 0.63; 95% CI: 0.53-0.75). FU: 14.4 mo. Radiologic PFS: 8.3 vs. 2.9 mo. HR: 0.40; 95% CI: 0.35-0.47 p < 0.0001)

Ra 223 (Six injections of 50 kBq/kg)- ALSYMPCA



Radium-223				
Parker, *et al.* 2013 [758]	radium-223	Placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	OS: 14.9 vs. 11.3 mo. (p = 0.002, HR: 0.61; 95% CI: 0.46-0.81). All secondary endpoints show a benefit over best standard of care

Cabazitaxel (25 mg/m2 IV q21 days for 10 cycles)



CABAZITAXEL				
Bahl, *et al.* 2013 [617]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	OS: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI: 1.33-3.33). FU: 25.5 months OS ≥ 2y 27% vs. 16% PFS: -
deBono, *et al.* 2010 [613]				OS: 15.1 vs. 12.7 mo. (p < 0.0001, HR: 0.70; 95% CI: 0.59-0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74; 95% CI: 0.64-0.86)

Please refer to Spine RT (SCORAD III: 8Gy X 1/ 20 Gy in 5#) at end of this section

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BCR

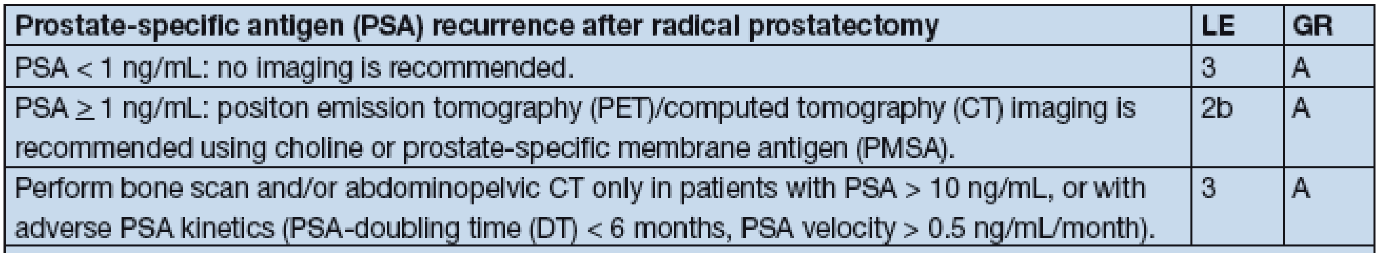
Post RP

Definition
Two consecutive PSA values above 0.2 ng/ml and rising

Clinical implication:
Incidence of 25-50% post RP. Of these, 30% develop a clinical recurrence and 6% die.
Pound et al (1999): 8 yrs from BCR to metastases, 5 yrs from metastases to death

High risk subgroup (Higher metastases and death)
>/=cT2
PSA>10 ng/ml
Gleason 8-10
BCR within 3 years
PSA doubling time <6 months
PSA velocity> 0.5 ng/ml/month

Evaluation



Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	GR
PSA < 1 ng/mL: no imaging is recommended.	3	A
PSA ≥ 1 ng/mL: positon emission tomography (PET)/computed tomography (CT) imaging is recommended using choline or prostate-specific membrane antigen (PMSA).	2b	A
Perform bone scan and/or abdominopelvic CT only in patients with PSA > 10 ng/mL, or with adverse PSA kinetics (PSA-doubling time (DT) < 6 months, PSA velocity > 0.5 ng/mL/month).	3	A

Choline PET
Combined sensitivity and specificity of 90% for all sites
<1 ng/ml: 25%, 1-2 ng/ ml: 40% and >2 ng/ ml: 70-100% detection rate of metastases

Ga68 PSMA PET
Detection rates of 58% and 76%have been reported for PSA ranges of 0.2-1 and 1-2 ng/mL
May not detect local recurrences as bladder tracer may obscure recurrence

TRUS and MRI are not very sensitive for local recurrence. Only 10-15% of patients have a positive CT. The mean PSA was 27 ng/ml and PSA velocity was 1.8 ng/ml/month in patients with a positive CT

Treatment
-RT to at least prostatic bed
-ADT (Continuous vs intermittent)
-Observation

RT dose of 76 Gy to bed
Should be initiated early at PSA of 0.5 ng/ ml: 60% will achieve undetectable PSA at 5 years
Three-fold improved cancer specific survival (CSS)
Salvage vs adjuvant RT showed similar outcomes in pT3N0M0 patients (80% PFS at 5 years)

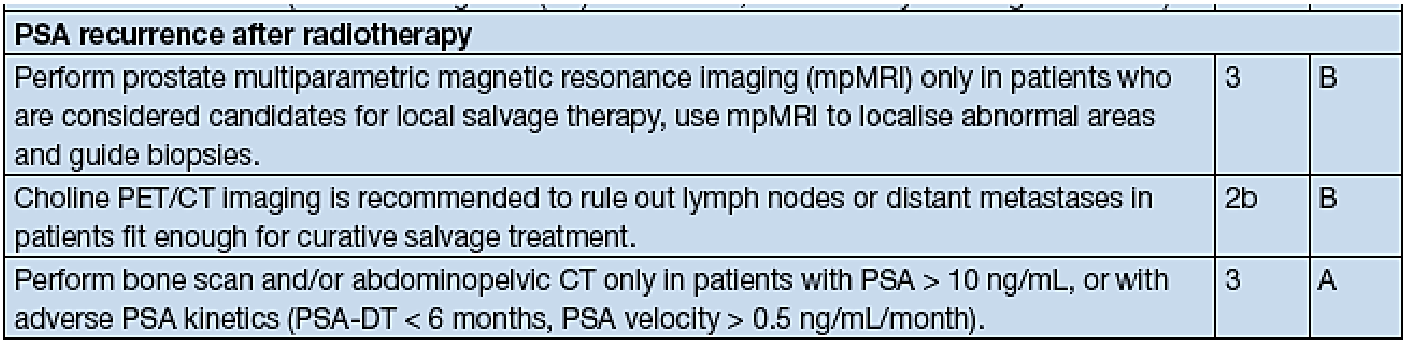
ADT improves outcome: RT +150 mg OD Bicalutamide for 2 yrs improved OS at 10 yrs from 78-82%
Also improved CSS: 97.7 vs 92.5% with a NNT of 17

In case of high risk factors: ADT and adjuvant RT recommended
In older, poor performance status patients with low risk disease: Salvage RT, avoid ADT
In older, poor performance status patients with high risk disease and <10 yrs expectancy: Observe

Post RT

Definition
Phoenix (preferred) : >2 ng/ml above nadir OR whenever salvage therapy initiated
ASTRO: 3 rises above nadir, 6 months apart

Evaluation



PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging (mpMRI) only in patients who are considered candidates for local salvage therapy, use mpMRI to localise abnormal areas and guide biopsies.	3	B
Choline PET/CT imaging is recommended to rule out lymph nodes or distant metastases in patients fit enough for curative salvage treatment.	2b	B
Perform bone scan and/or abdominopelvic CT only in patients with PSA > 10 ng/mL, or with adverse PSA kinetics (PSA-DT < 6 months, PSA velocity > 0.5 ng/mL/month).	3	A

Mandatory to obtain biopsy proof of recurrence with mpMRI and TRUS guided biopsy before treatment

Treatment

-Salvage radical prostatectomy (SRP)
-Brachytherapy
-Cryotherapy and HIFU
-ADT
-Observation

SRP

10 yr PFS: 25-50%, CSS: ~75%, OS: ~70%. Those with + margins/ SV invasion did worse (CSS of 50%)
Should be considered only for low risk, fit patients with >10 yrs life expectancy due to high morbidity
Complications:

Anastomotic stricture : 50% (5%)
Retention : 25% (3%)
Urinary fistula/ abscess : 5% (<1%)
Rectal injury : 10% (1%)
ED : 100% (20-90%)
Incontinence : 20-90% (20%) Brackets: Primary RP complication rates

To be performed only in high volume centres

Cryotherapy

5 yr PFS of 60%, response seen in 50% patients
Should be considered for low risk with >10 yrs life expectancy due to high morbidity
Complications:

ED 90%
Incontinence 30%
Pelvic pain 40%
Sx for local complications 4%
` Rectal fistula 1%

HIFU

Experimental, PFS 60% at 2 yrs
Should be considered for low risk with >10 yrs life expectancy due to high morbidity

Brachytherapy

5 yr PFS of 50-70%, LDR (140 Gy) or HDR (32 Gy, 4#)
Almost half the patients will have grade 2 urinary side effects
Should be considered for low risk with >10 yrs life expectancy due to high morbidity

ADT

Indicated in high risk disease for patients >10 yrs life expectancy

SCORAD III: Randomized noninferiority phase III trial of single-dose radiotherapy (RT) compared to multifraction RT in patients (pts) with metastatic spinal canal compression (SCC).

Abstract:

Background: SCC is a common complication of metastatic cancer. Most pts receive RT to improve neurological function and to relieve pain. There is no standard schedule (RT ranges from single dose 8Gy to 40Gy in 20 fractions). SCORAD III was conducted to show whether a single fraction is as effective as multifraction RT without compromising patient outcomes.

Methods: Pts from 43 UK and 4 Australian sites were randomized (1:1) to receive external beam spinal canal RT as a single dose of 8Gy or 20Gy in 5 fractions.

Eligible pts had spinal cord or cauda equina (C1-S2) compression confirmed by MRI/CT scan, treatable within a single radiation field, life expectancy >8 weeks (wks), no previous RT to the same area.

Primary endpoint was AS at wk 8: graded 1 (full function) to 4 (no/flicker motor power). The noninferiority margin was 11% for comparing the proportion of patients with AS 1 or 2 at wk 8 (whether maintained from baseline or improved from AS 3-4).

Results: 688 pts were randomized Feb 2008 to Apr 2016 (n=345 single dose, n=343 multifraction). 73% were male; median age 70 years; ambulatory with/without walking aids 66%; 44% prostate, 18% lung, 11% breast, 11% gastrointestinal. Baseline characteristics were balanced.

69.5% (114/164 pts evaluable at wk 8) single dose vs. 73.3% (129/176) multifraction had AS 1-2 at wk 8 (risk difference: -3.78%, 90%CI -11.85 to 4.28). Importantly, overall survival (OS) was very similar: median OS 12.4 wks single dose vs. 13.7 multifraction, (hazard ratio 1.02 [95%CI 0.86-1.21], p=0.81).

Proportion of pts with adverse events was similar for grade 3-4 (20.6% single dose vs. 20.4% multifraction), but grade 1-2 events were lower with single dose (51.0% vs. 56.9%)

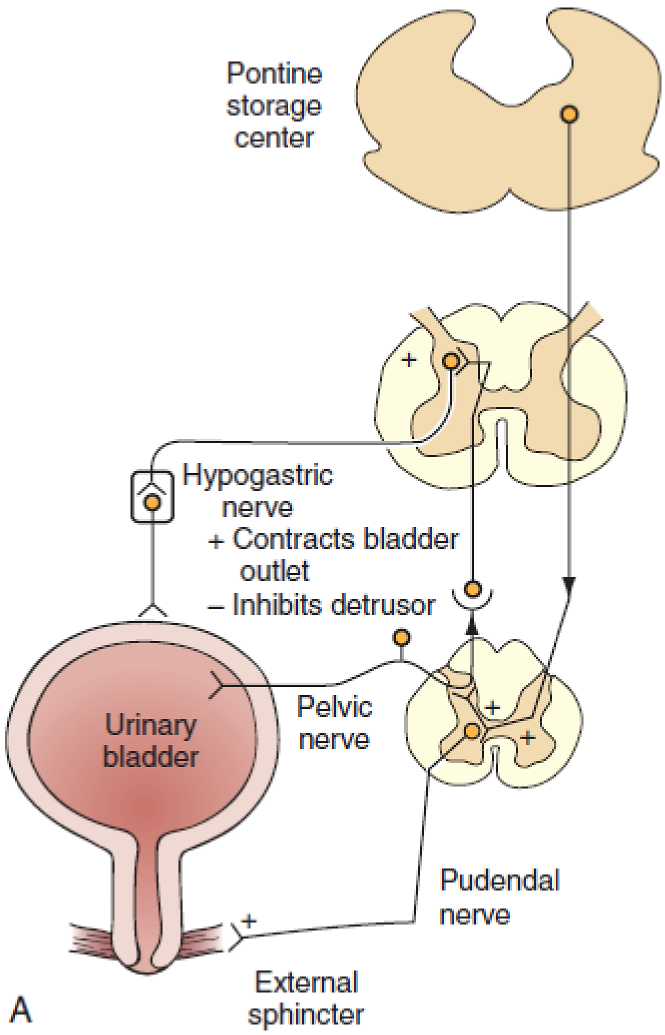
. Conclusions: Using a single dose of 8Gy in pts with metastatic SCC was as effective as multiple fractions for AS at 8 wks and OS. We now recommend using single dose RT in this setting, with the major benefit of requiring only a single instead of multiple hospital visits, important when considering the short survival in these pts.

MALE CONTINENCE, SLINGS IN POST-PROSTATECTOMY INCONTINENCE

Male continence

Role of bladder as a low pressure storage organ

Neural component



As the bladder is filled, afferent sympathetic signals travel via the hypogastric plexus to the pontine storage centre which stimulates contraction of the external sphincter via the pudendal nerve.

Sympathetic stimulation and parasympathetic inhibition produces relaxation of the detrussor (beta receptors) and contraction of the bladder neck and lissosphincter (alpha receptors).

Any sudden increase in abdominal pressure causes further activation of the pudendal nerve leading the contraction of the external sphinter and pelvic floor and the pressures rise well above 40 cm water. This is called the guarding reflex.

Anatomic component

Intra-peritoneal position of bladder dome permits unimpeded expansion.
Multi-layered mucosal layer of bladder promotes expansion with filling, collapse with emptying.
Poor coupling between detrusor smooth muscle cells dissipates aberrant contractions.
Extracellular matrix composition promotes minimal change in bladder pressure
High elastin to collagen ratio. Collagen type I is major collagen subtype in the compliant bladder.

Role of bladder outlet

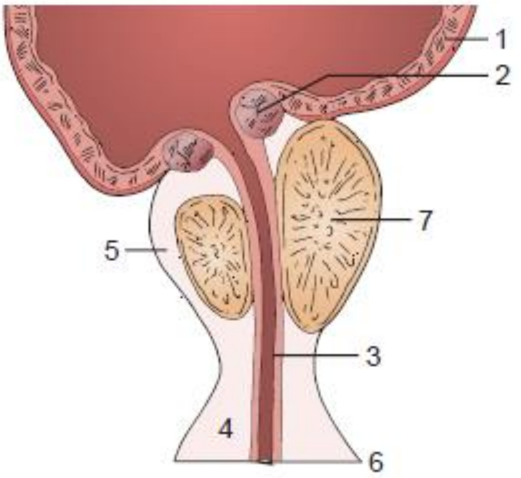


Figure 74-8. **Male urethral sphincter complex. 1, Bladder musculature. 2, Proximal part of internal sphincter. 3, Distal part of internal sphincter. 4, Rhabdosphincter. 5, Prostatic part of rhabdosphincter. 6, Perineal membrane. 7, Prostate.**

Urethral mucosa and submucosa

Urethral mucosal longitudinal folds and well-vascularized spongy submucosal layer allow for both distensibility and creation of a seal that enhances urethral closure during bladder filling.

Proximal/ smooth/ lissosphincter

3-4 cm in length.

Thick inner longitudinal and thin outer circular layer of smooth muscles and a thinner lamina propria than detrusor.

Cylinder completely surrounding the urethra from the bladder neck to the perineal membrane.

Prostatic smooth muscle also contributes to outlet resistance.

Innervation: Alpha adrenergic sympathetic fibres

Distal/ striated/ rhabdosphincter

1.5 to 2.4 cm in length

Surrounds the membranous urethra.

The muscle fibers extend from the base of the bladder to the membranous urethra.

Horseshoe/ omega shape around membranous urethra; deficient posteriorly

They are predominantly type I slow-twitch fibers.

The peri-urethral striated muscles of the pelvic floor lie external to the striated urethral muscle

Innervation: Sympathetic and Pudendal. The autonomic nerves enter at the 5 and 7 O'clock positions, while the somatic nerves enter at the 9 and 3 O'clock positions.

Pelvic floor musculature

Fast-twitch fibers contribute to the ability to transiently enhance voluntary closure during stress
Pubourethralis supports the prostatic urethra

Supporting ligaments

Anterior puboprostatic ligaments suspend the prostate from the pubis.

Posterior support from the perineal body

Slings for male incontinence

Indications

Mild/ moderate incontinence

Adequate detrussor contractility with normal compliance

Impaired cognition/ manual dexterity

Patient preference

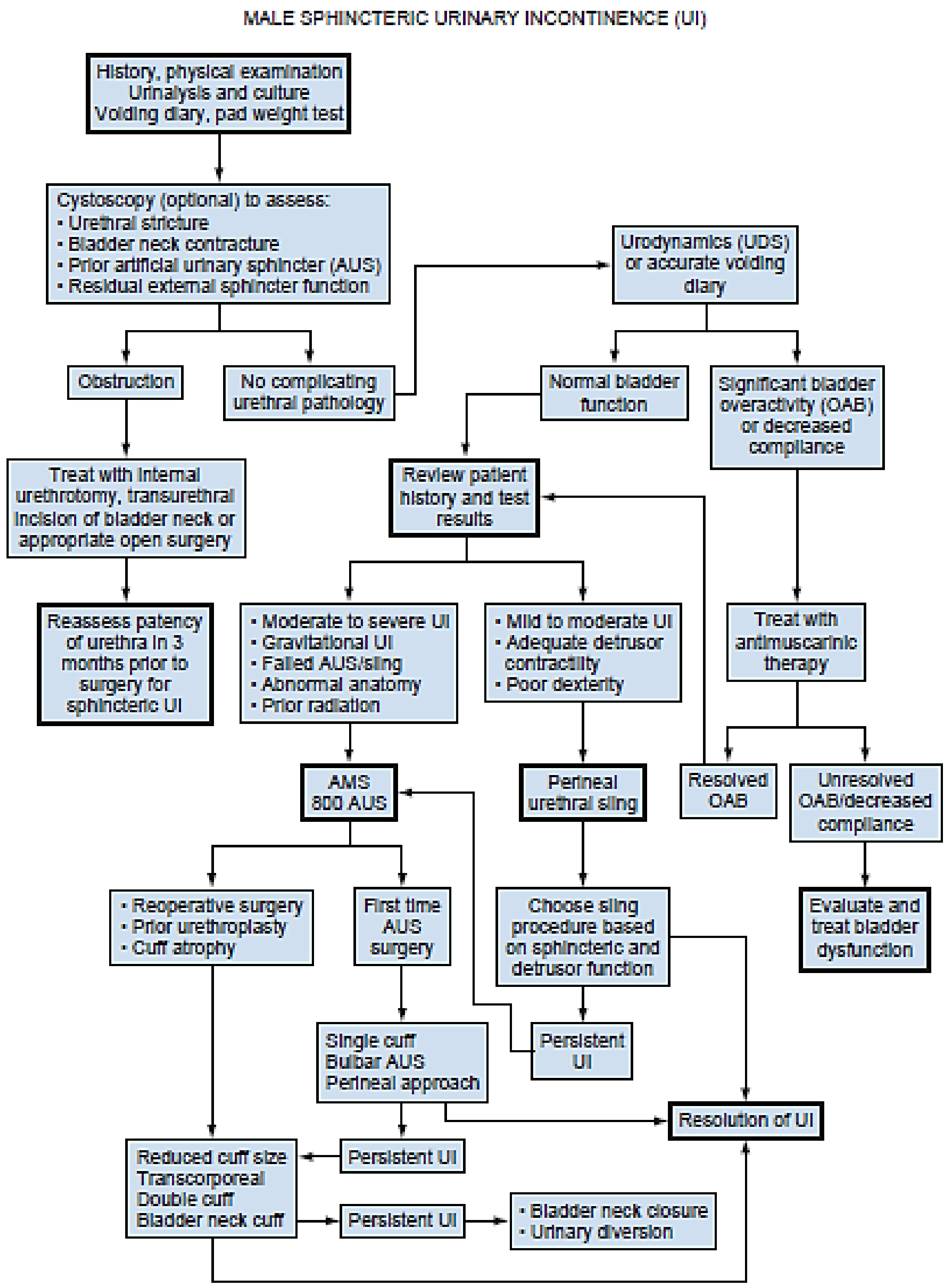
Contraindications

Severe/ gravitational incontinence

Prior failed procedure for UI

Abnormal anatomy

Prior radiation


MALE SPHINCTERIC URINARY INCONTINENCE (UI)
History, physical examination
Urinalysis and culture
Voiding diary, pad weight test
Cystoscopy (optional) to assess:
• Urethral stricture
• Bladder neck contracture
• Prior artificial urinary sphincter (AUS)
• Residual external sphincter function
Urodynamics (UDS) or accurate voiding diary
Obstruction
No complicating urethral pathology
Normal bladder function
Significant bladder overactivity (OAB) or decreased compliance
Treat with internal urethrotomy, transurethral incision of bladder neck or appropriate open surgery
Review patient history and test results
Reassess patency of urethra in 3 months prior to surgery for sphincteric UI
• Moderate to severe UI
• Gravitational UI
• Failed AUS/sling
• Abnormal anatomy
• Prior radiation
• Mild to moderate UI
• Adequate detrusor contractility
• Poor dexterity
Treat with antimuscarinic therapy
AMS 800 AUS
Perineal urethral sling
Resolved OAB
Unresolved OAB/decreased compliance
• Reoperative surgery
• Prior urethroplasty
• Cuff atrophy
First time AUS surgery
Choose sling procedure based on sphincteric and detrusor function
Evaluate and treat bladder dysfunction
Single cuff
Bulbar AUS
Perineal approach
Persistent UI
Resolution of UI
Reduced cuff size
Transcorporeal
Double cuff
Bladder neck cuff
Persistent UI
Persistent UI
• Bladder neck closure
• Urinary diversion

Algorithm for male post-prostatectomy incontinence

Transobturator (Advance)

Reposition and lengthen the membranous urethra and elevate the bulb 3-4 cm cephalad

Perineal incision, open bulbospngiosus, dissect spngiosum upto perineal body.

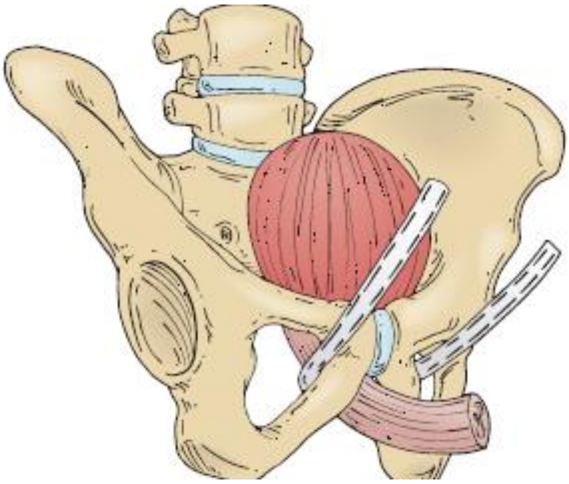
Inferior margin of adductor longus, stab 1 fingerbreadth below, locate obturator foramen with spinal needle

Use left/ right helical passing device from thigh into obturator foramen and out into perineum medial to corporal body, as close to the ramus as possible

Attach mesh to passing device and pull out of obturator foramen without tension

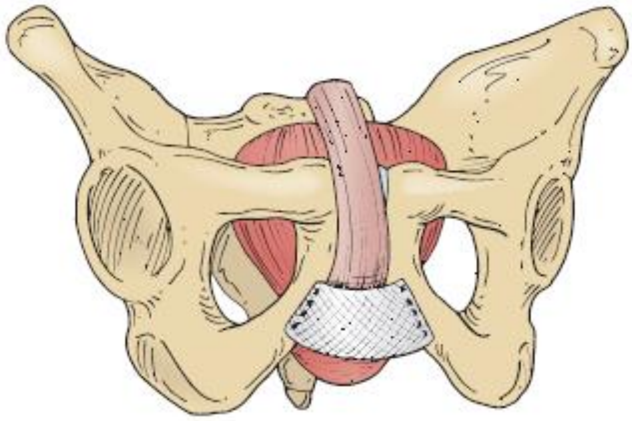
Tensioning under cystoscopic vision

Four to six sutures to tack mesh to spongiosum



Bone anchored slings (Invance)

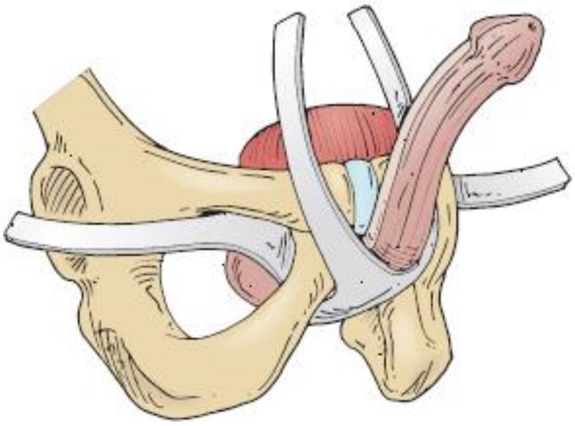
- Outside bulbospongiosus and tied to with 3-4 Titanium screws drilled into inferior pubic ramus.
- Bulbar urethral compression against the symphysis
- 4X7 cm usual dimension
- Tensioning under cystoscopic guidance, intra-operative cough test



Quadratic fixation devices (Virtue)

Transobturator bulbar elevation as well as prepubic arms for compression of the bulb

For more severe cases of incontinence after radical prostatectomy



Results

76 % success (patients dry) while 13% improved.

Complications

Self-limiting pain in 74% up to 3 months

Urinary retention can persist for weeks

Erosion/ infection: 2-15%

Need for revision: 2-4%

Osteitis pubis

ANTICHOLINERGICS

Mechanism of action

Bladder filling causes release of Acetylcholine (Ach) from urothelium and sub-urothelial tissue.

This in turn stimulates the afferent nerves (A delta and C fibres) producing the sensation of filling and urgency.

Filling also increases the resting tone of detrussor both due to direct stimulation by locally released Ach as well as due to afferent nerve stimulation.

It has been noted that anticholinergics (AC) not only reduce urgency and urgency incontinence, they also improve compliance, time to first detrussor overactivity (DOA) and reduce the amplitude of DOA.

Classification

Tertiary Amines (Low molecular weight, lipophilic, pass into CNS)

Tolterodine

Oxybutynine

Darifenacin

Solifenacin

Fesoterodine

Imidafenacin

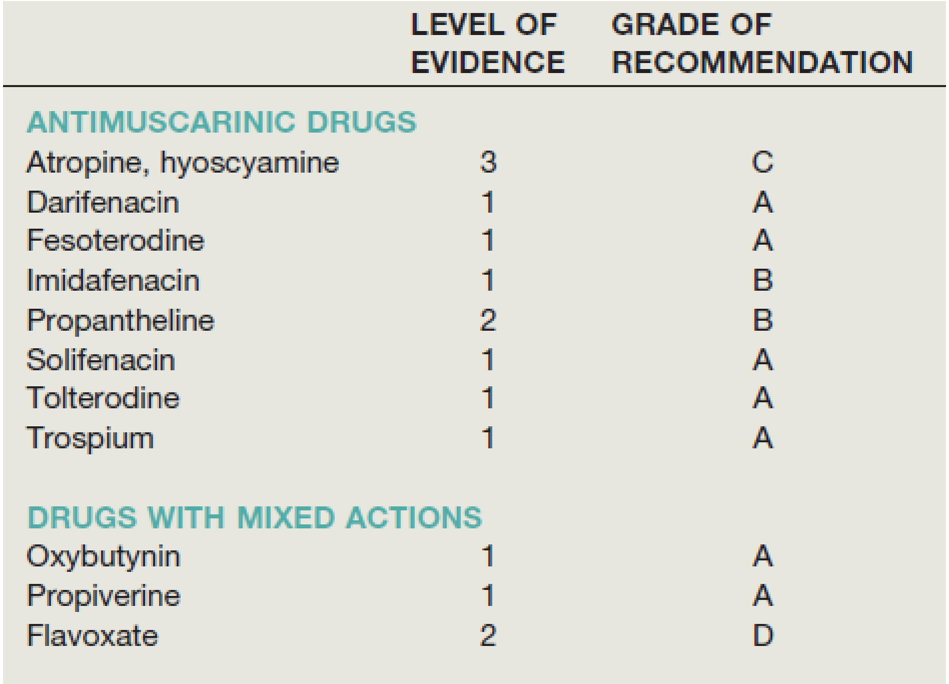
Propiverine

Quartenary amines (High molecular weight, not lipophilic, do not pass into CNS)

Trospium

Propantheline

Evidence in favour of AC



	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
ANTIMUSCARINIC DRUGS		
Atropine, hyoscyamine	3	C
Darifenacin	1	A
Fesoterodine	1	A
Imidafenacin	1	B
Propantheline	2	B
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
DRUGS WITH MIXED ACTIONS		
Oxybutynin	1	A
Propiverine	1	A
Flavoxate	2	D

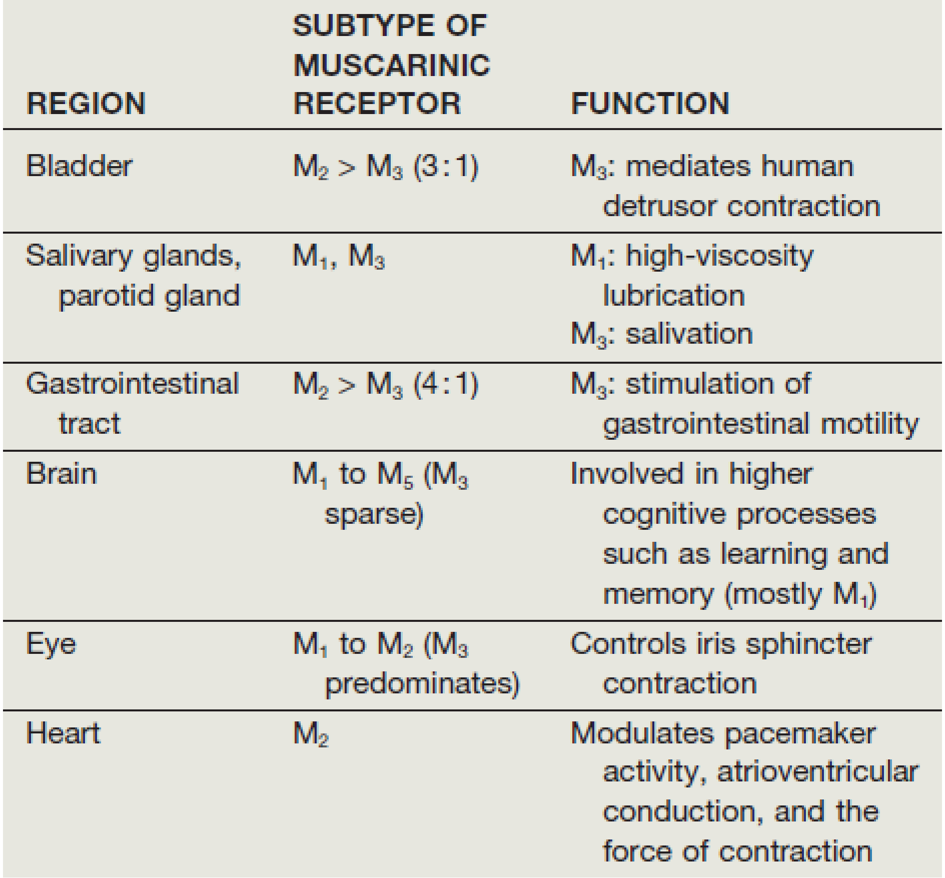
All drugs except Flavoxate, Propantheline and Atropine have been proven to be effective in RCTs

Common pharmacology

Orally absorbed

Metabolized by cytochrome P450 enzymes (CYP 3A4 and 2D6) in liver, very minimal urinary excretion except Trospium which is secreted by renal tubules

ADR



REGION	SUBTYPE OF MUSCARINIC RECEPTOR	FUNCTION
Bladder	$M_2 > M_3$ (3:1)	M_3: mediates human detrusor contraction
Salivary glands, parotid gland	M_1, M_3	M_1: high-viscosity lubrication M_3: salivation
Gastrointestinal tract	$M_2 > M_3$ (4:1)	M_3: stimulation of gastrointestinal motility
Brain	M_1 to M_5 (M_3 sparse)	Involved in higher cognitive processes such as learning and memory (mostly M_1)
Eye	M_1 to M_2 (M_3 predominates)	Controls iris sphincter contraction
Heart	M_2	Modulates pacemaker activity, atrioventricular conduction, and the force of contraction

Based on the distribution of Ach receptors, the common ADR are:

- Dryness of mouth (Most common)
- Constipation
- Blurring of vision
- Increase in heart rate
- Polymorphic ventricular tachycardia (Due to inhibition of cardiac hERG K channels via M2 receptors leading to cardiac depolarization and increased activity of myocytes)
- Headache, impaired cognition and memory (VPCs and cognitive impairment are rare)

Specific drugs

Name	Formulation/ Bioavailability	Active metabolite	Receptor selectivity	T1/2 (hrs)	Time to efficacy	ADR incidence	Dose
Oxybutynin	Oral- IR, ER Transdermal (TD) Transdermal gel (G) Intravesical/ rectal	NDO	M1,3>M2	2	-	Overall 80% Pruritus 16% Erythema (8%)	IR-5 mg TID/ q6h ER-5-10 mg OD TD-3.9 mg OD G-1 gm OD(4 mg)
Tolterodine	IR, ER	5-HMT	None	2-3	-	Dry mouth: 10-30% Constipation 5%	IR-1-2 mg BD ER-2-4 mg OD
Darifenacin	IR, ER	UK-148993	M3	14-16	6-8 days	Dry mouth 0.5% Constipation 2%	7.5-15 mg OD
Solifenacin	Single formulation	-	M3>M2,1	45-68	7 days	Dry mouth 6% Constipation 6%	5-10 mg OD
Fesoterodine	Single formulation	5-HMT	None	7-9	-	Dry mouth 30% Constipation 5%	4-8 mg OD
Imidafenacin	Single formulation	-	M1,3>M2	3	3 days	Dry mouth 40%	0.1-0.2 mg/ day
Trospium	IR, ER, intravesical	-	None	20	-	Dry mouth 20% Constipation 10% Headache 6%	ER-20 mg OD IR-20 mg TID
Propiverine	Single formulation	-		11-14	-	14% dry mouth, constipation, blurring and tachycardia	15 mg BD

NDO: N-desethyl oxybutynin, 5-HMT: 5-Hydroxy methyl Tolterodine

Oxybutynin

ER: Osmotic system to release the drug at a controlled rate over 24 hours primarily into the large intestine. Absorption is not subject to first-pass metabolism in the liver. Reduction in metabolism improves dry mouth. Also noted with TD and G.
Maximum dose: 20 mg OD for IR and 30 mg OD for ER.
Oxybutynin intravesical also has a local anaesthetic action

Tolterodine

Highly lipophilic, no cognitive side effects as it does not cross blood brain barrier
More affinity for bladder than salivary glands
OBJECT
OPERA
ACET

Darifenacin

High first pass- only 3% urinary excretion, rest in bile after CYP3A4 metabolism
It is a ligand for P glycoprotein- Is pumped out of eye and CNS- No accommodation/ CNS side effects

Fesoterodine

Converted to active metabolite 5-HMT by liver
70% renal excretion

Trospium

760% excreted unchanged in urine
Is a P-glycoprotein substrate- Is pumped out of eye and CNS, limited CNS permeability as it is a quartenary ammonium compound
More effective than oxybutynin with fewer side effects

ALPP

Measure of ability of sphincter to resist increase in abdominal pressure
Pves at which leak occurs with rise in Pabd in the absence of detrussor contraction.
Can be demonstrated only in the presence of SUI.
Standing position, vesical/ abdominal pressure line, include the baseline Pves in final reading.
Straining (ALPP) or valsalva (VLPP) or cough (CLPP). Usually **CLPP>VLPP>ALPP**
Larger the catheter, lower the ALPP.

Start at 150 ml, 50 ml increments till leak occurs.
If no SUI at capacity (15% women, 35 % men after prostatectomy), remove urethral line
Cutoffs: **<60 cm water indicates intrinsic sphincter deficiency, 60-90 equivocal and >90 no ISD**.
However, in the absence of urethral hypermobility and SUI, it is due to ISD irrespective of ALPP.
Surgery for SUI has poorer outcomes if ALPP < 60 cm water.

DLPP

Lowest Pdet at which urine leak occurs during filling in the absence of abd/ detrussor contraction
Measure of urethral resistance
Of significance in a poorly compliant bladder: Lower DLPP, leak occurs at safe pressures
Useful in UMN bladder, multiple bladder operations, RT, TB: Poor compliance/ DO with DESD
McGuire et al (1981): >40 cm water DLPP: HUN/ VUR in 85% patients with myelodysplasia, causes upper tract damage
Rx: Anticholinergics, BNI, augmentation, urinary diversion

UDS in SUI

Not indicated in isolated SUI
May be considered if:
- Diagnosis in doubt
- Storage symptoms/ mixed SUI
- High PVR
- Prior failed Sx
- Neurological disease/ DM/ prior RT
- To counsel patients prior to invasive, irreversible operations

Differentiate between incontinence due to detrussor/ outlet, storage/ voiding dysfunction
Eyeball UDS may be used:
- Lithotomy, Foley's, PVR
- Bladder filled with 60 ml syringe held upright
- Document first sensation, first desire and normal desire
- Height of meniscus in syringe=Pves. Sudden rise=DOA
- Abdominal contribution cannot be recorded
- Catheter removed and cough test for SUI

Record ALPP and UDS-SUI:
<60 cm water indicates intrinsic sphincter deficiency, 60-90 equivocal and >90 no ISD.
However, in the absence of urethral hypermobility and SUI, it is due to ISD irrespective of ALPP.
Surgery for SUI has poorer outcomes if ALPP < 60 cm water

Rule out underactive detrussor, low compliance, dysfunctional voiding/ DESD/ PBNO and diverticula/ reflux
Poor accuracy: PPV 56 and 79% for pure and mixed SUI for UDS
PPV 55 and 91% for pure and mixed SUI for cough test

Issues with reproducibility, does not predict outcome or need for subsequent surgery

However 20% patients may have findings that changes management
Pre-op UDS-SUI is predictive of post-operative SUI after correction of pelvic organ prolapse.
(Rates: Occult SUI: 40-80%, de-novo SUI after POP repair: 10-50%)

RCTs required to address the need for UDS in SUI

MID URETHRAL SLING EXPOSURE/ PERFORATION

Exposure (=vaginal erosion)
Seen in 0.5-8%
Seen in few weeks to months post-op
Symptoms: Pain, bleeding/ discharge from vagina, storage LUTS, UTI, haematuria, dyspareunia, palpable rough surface.
Higher exposure with smaller pores, diabetes, single midline (as compared to bilateral lateral) incision
Asymptomatic exposure without pain or sexual dysfunction may be managed conservatively.
Small area exposed: Conservative, local oestrogens, antibiotic cream and trimming + vaginal closure
If these fail, excision of exposed mesh, antibiotic solution irrigation and closure of vaginal flaps
Continence is usually maintained in spite of mesh removal due to fibrosis.

Trocar injury
Trocar injury to urinary tract is a benign event (3-24%) during mesh placement.
Retropubic> trans-obturator slings
Managed with CBD for one week

Perforation (=erosion into bladder/ urethra)
Urethra
Always needs specialist referral
0-0.6% incidence
Risk factors (urethral):
    Tension
    Ischaemia (post RT/ dissection near urethra)
    Iatrogenic injury during mesh placement
    Traumatic urethral dilatation
    Rolling of sling causing pressure necrosis
Voiding/ storage LUTS, UTI, need for dilatation, retention, haematuria
Mesh seen on cystoscopy/ urethral narrowing with proximal dilatation seen on MCU
Endoscopic excision with laser/ endoscopic scissors
Transvaginal excision and repair with Martius interposition
Prevent by interposing martius flap in case of tenuous repairs

Bladder
Bladder erosion is due to unrecognized cystotomy
Storage LUTS, haematuria, UTI, incontinence, encrustation/ stone formation
Diagnosed on cystoscopy
Small perforation: Transurethral excision with Ho-YAG or transvesical excision with lap instruments
Larger perforations on dome: Open excision and repair with omental interposition

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AMBULATORY URODYNAMICS

Functional test of LUT using natural filling that reproduces daily activities/ symptomatology
If standard UDS is inconclusive/ additional obtained information will affect treatment
Patient counselling:
    How the test works
    Diary to record symptoms
    How to identify catheter displacement or hardware failure
    Provocative manoeuvres for DOA and SUI.
Microtip transducer catheters perurethral and in the rectum, securely fixed and connected to recorder

Absorbent electronic diaper can record leaks

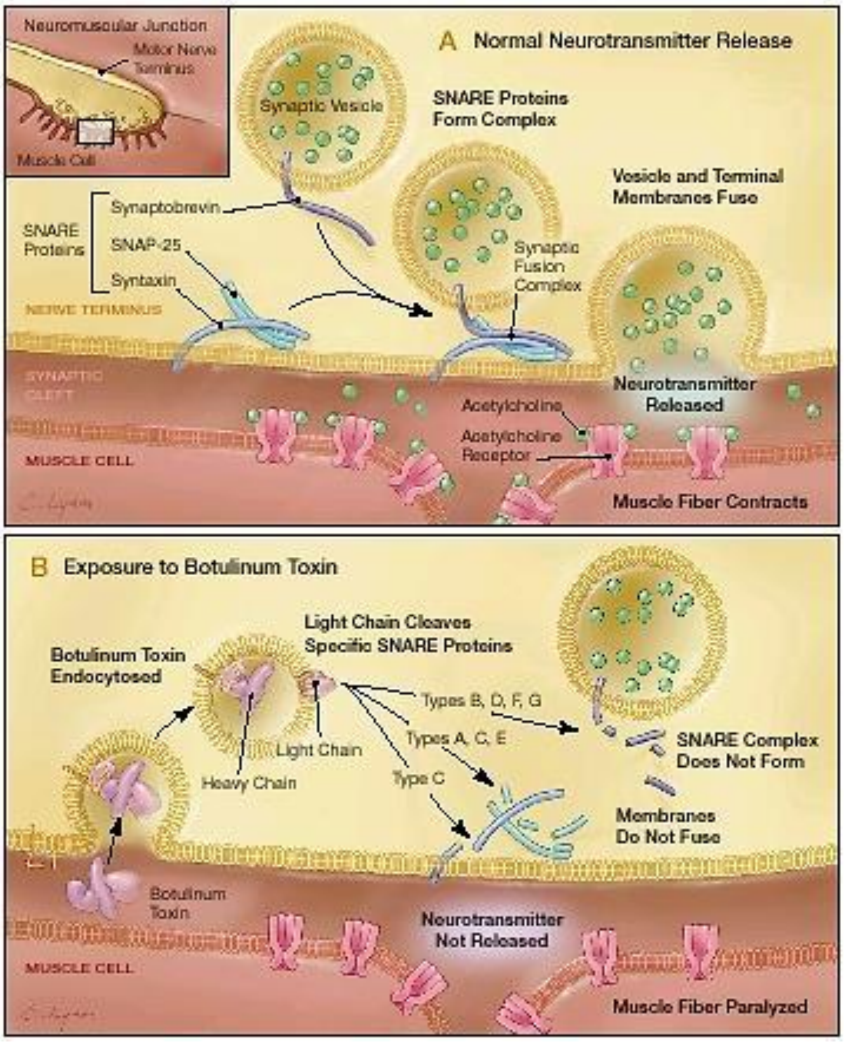
Increased sensitivity for DOA, incontinence as more time is given
Identified 77% of female SUI missed on conventional UDS
Sensitivity for neurogenic DOA was 85% (75% conventional)

Multiple artefacts due to movement and straining, time consuming and difficult to interpret
No studies on reproducibility/ reference standards

DULOXETINE
Selective serotonin uptake inhibitor
Improves sphincteric activity during filling as well as bladder volume in the cat acetic acid model
Lowers incontinence episodes, increases time between voids and QoL
80 mg once daily
Nausea, dizziness, dry mouth, constipation, fatigue, insomnia, CYP3A4 inhibition
Useful in SUI and mixed SUI

BOTULINUM TOXIN
High doses without systemic side effects is the advantage of intravesical therapy
Useful in those who cannot tolerate oral therapy due to side effects or have refractory symptoms
Neurotoxin produced by *Clostridium botulinum*
Seven subtypes: Subtype A has the longest action and is clinically useful. B is also used
Wrapped in different proteins: Botox, Dysport, Xeomin and Prosigne (All subtype A)
Botox and Xeomin are thrice as potent as Dysport. Most studies on Botox
Heavy and light chain with disulphide bond

Mechanism of action:



Effect on efferents
Binds to Synaptic Vesicle protein 2 (SV 2) via the heavy chain, internalized by presynaptic terminal
The light chain is cleaved from the molecule and passes into cytoplasm where it cleaves SNAP-25 (Synaptosome Associated Protein-25)
This inactivates the SNARE complex
This prevents fusion of vesicles to cytoplasmic membrane which prevents Acetyl choline release
Subtype B cleaves VAMP (Vesicle Associated Membrane Protein) instead of SNAP-25

Effect on afferents
Prevents release of
  Substance P
  Glutamate
  Calcitonin gene related peptide (CGRP)
  Neuropeptides
Prevents transport of TRPV1 (Transient Receptor Potential channel) from vesicles to nerve ending

It also reduces Nerve growth factor (NGF) and Brain derived Neurotrophic Factor (BDNF) which affects plasticity of peptidergic afferent neurons

Uses:
OAB, NDO (spinal trauma, multiple sclerosis, meningomyelocoele), DESD, dysfunctional voiding
Two to fourfold improvement over placebo in frequency, urgency and incontinence episodes in RCTs
Equivalent to Solifenacin (5-10 mg)/ Trospium ER (60 mg) in reducing UUI in women with OAB
Improves compliance, DOA and cystometric capacity on UDS

Dose: 100 U OAB, 200 U neurogenic DOA and 100-200 units DESD. 10-12 U/kg children
  Lasts 6-12 months

Injection technique:
Store vial at – 5 degrees, use reconstituted with 10 ml saline: Use within 24 hours
30-60 ml of 1-2% lignocaine in bladder for 30-60 min + urethral lignocaine/ spinal anaesthesia
Flexible or rigid cystoscope (Rigid easier)
Injection template (1 cm apart, 2 mm depth using a 22-27 mm long/ 4-8 mm gauge needle)

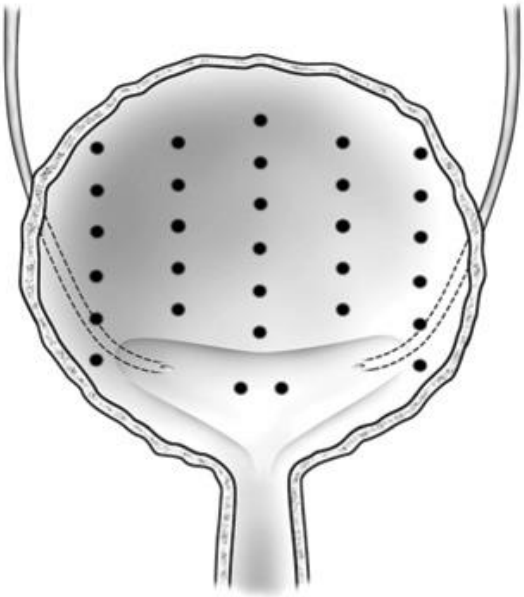


***Figure 2** – University of Chicago botulinum toxin injection protocol (Reprinted with permission from Elsevier Inc, Urology, Rapp DE et al., ref. 13).*

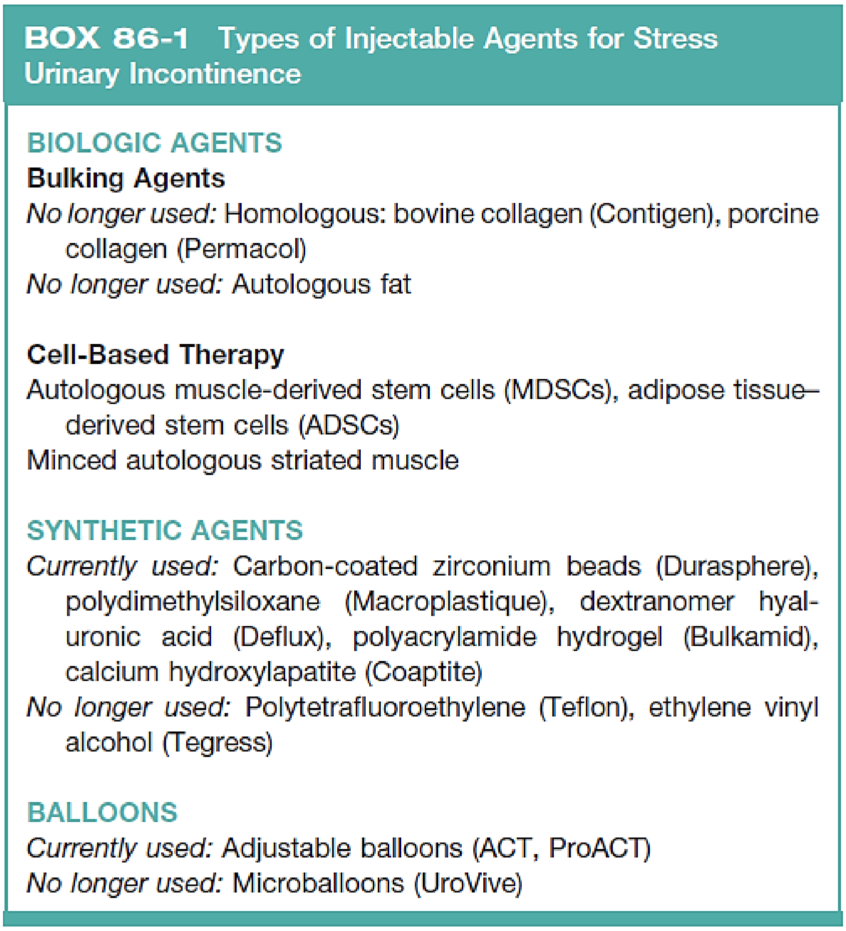
Adverse effects: Dysuria (10%), UTI (5%), retention
  Need for CIC (100 U-5%, 200 U-30%, 300 U-45%)

INJECTION THERAPY FOR SUI

Ideal agent
Biocompatible
Does not migrate and conserves its volume with time (>110 um particle size)
Non allergenic
Non carcinogenic
No fibrosis/ inflammation
Does not affect future surgery

Indications (Meant for ISD)
Poor surgical risk
Elderly
Unwilling for surgery
On anticoagulation
Minor SUI post sling surgery
Minor SUI with exercise
Underactive detrussor and SUI
Family not complete

Agents for injection therapy



BOX 86-1 Types of Injectable Agents for Stress Urinary Incontinence

BIOLOGIC AGENTS

Bulking Agents

No longer used: Homologous: bovine collagen (Contigen), porcine collagen (Permacol)

No longer used: Autologous fat

Cell-Based Therapy

Autologous muscle-derived stem cells (MDSCs), adipose tissue–derived stem cells (ADSCs)

Minced autologous striated muscle

SYNTHETIC AGENTS

Currently used: Carbon-coated zirconium beads (Durasphere), polydimethylsiloxane (Macroplastique), dextranomer hyaluronic acid (Deflux), polyacrylamide hydrogel (Bulkamid), calcium hydroxylapatite (Coaptite)

No longer used: Polytetrafluoroethylene (Teflon), ethylene vinyl alcohol (Tegress)

BALLOONS

Currently used: Adjustable balloons (ACT, ProACT)

No longer used: Microballoons (UroVive)

Workup

History: Type, severity, frequency of incontinence with use of questionnaire
Storage LUTS, UTI, haematuria, prior RT or operations, allergies

Examination: Lithotomy for atrophic vaginitis, prolapse, cervical/ pelvic mass, VVF
Standing/ sitting on a comfortably full bladder for SUI/ prolapse
Q tip test- Cotton tipped swab in urethra- strain- more than 30 degrees deflection in horizontal axis indicates hypermobility of urethra

Investigations: Bladder diary, Urine microscopy, PVR mandatory
Pad test, ultrasound, cystoscopy, UDS depending on patient

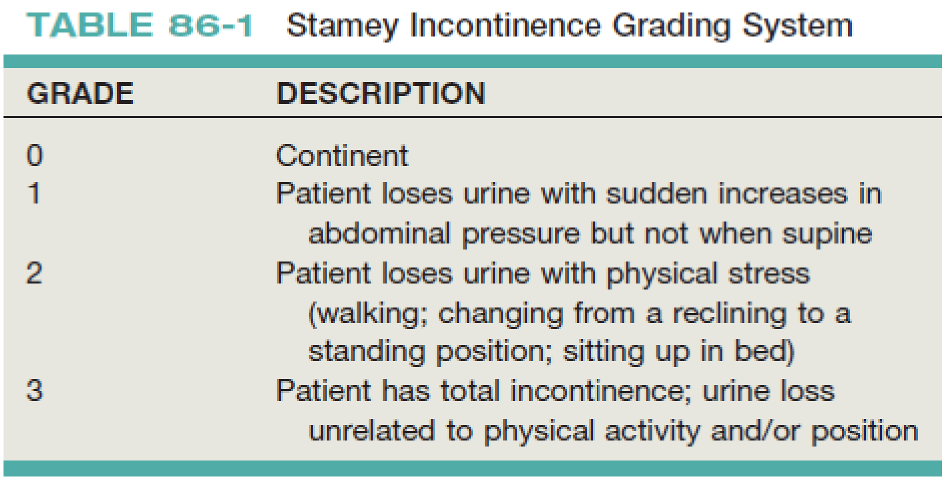
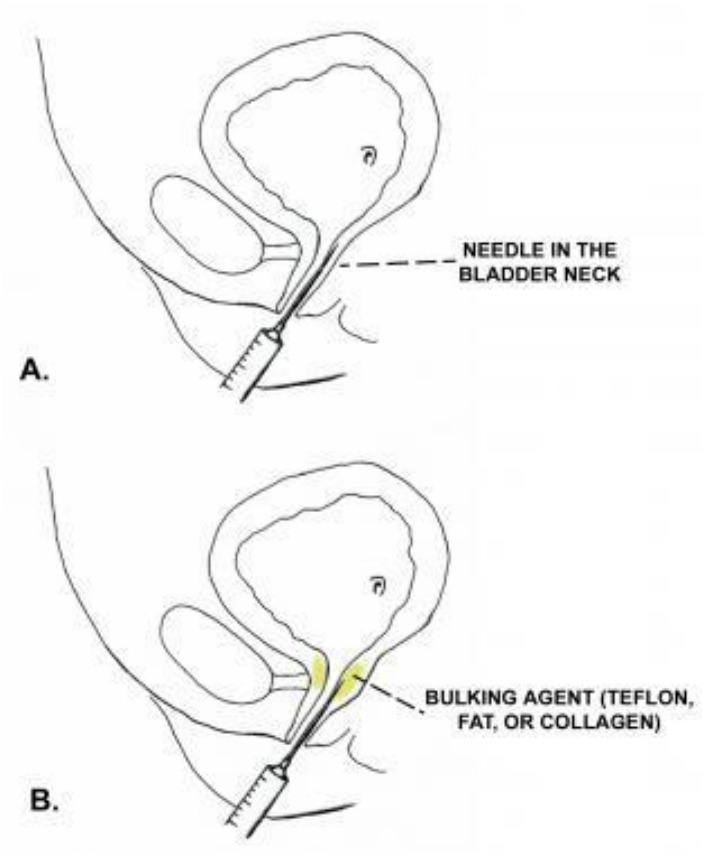


TABLE 86-1 Stamey Incontinence Grading System

GRADE	DESCRIPTION
0	Continent
1	Patient loses urine with sudden increases in abdominal pressure but not when supine
2	Patient loses urine with physical stress (walking; changing from a reclining to a standing position; sitting up in bed)
3	Patient has total incontinence; urine loss unrelated to physical activity and/or position

Injection technique
Paraurethral/ transurethral
2-3 ml of 1-2 % lignocaine injected at either side of EUM, 4 mm lateral at 3/9 or 4/8 O’ clock (26 G)
Syringe with bulking agent introduced either paraurethral, parallel to cystoscope or via cystoscope
Injected into lamina propria/ submucosa at bladder neck/ proximal urethra until mucosal coaptation like the lateral lobes of prostate is seen at 3/9 or 4/8 O’ clock
If cystosope used: 20 F, 30 degree. 22 G needle, 1 cm long tip. Injected at 45 degrees into mucosa.
SUI is checked on table and additional volume injected if needed
Circumferential injection may give better results
Many require repeat injection on f/u at 1-4 wks. Timing depends on the agent used.


NEEDLE IN THE BLADDER NECK
A.
BULKING AGENT (TEFLON, FAT, OR COLLAGEN)
B.

Agent	Contains	Particle/ needle size and inj volume	Results	Specific ADR	Comments
Cross linked bovine collagen	Bovine collagen- 95% type I and 5% type III	22 G, 2-3 ml/ syringe- 3 syringes	Dry: 70% at 1 yr, 60% at 2 yrs and 45% at 3 yrs	Allergy	Allergy in 3%. Needs skin test 30 days before injection
Durasphere	Carbon coated Zirconium beads in 2.8% beta glucon gel	212-500 um 90-212 um 18 G	60-80% pts show improved grade of SUI at 2 yrs	Particle migration when injected under pressure (viscous)	-
Macroplastique	Polidimethoxylsiloxane	100-450 um, 16 G, 2.5 ml	60% improved at 1 year	-	30% reinjection rate
Bulkamid	Polyacrylamide hydrogel 2.5%	23 G, 1 mlX2	60% improved, 50% dry at 1 year	-	40% reinjection rate. Used in contact lens
Coaptite	Calcium hydroxylapatite in carboxymethylcellulose gel	100 um, 21 G, 1 ml	60% improved at 1 year	Vaginal erosion, granulomas	Used in Ortho, dental, vocal cord augmentation
Deflux/ Implacer	Dextranomer in hyaluronic acid gel	80-250 um, 2.8 ml	76% improved at 1 year	Inferior to collagen with pseudoabscess formation	Withdrawn
Autologous cells	Stem cells: Bone marrow, adipose derived, umbilical cord blood, skeletal muscle	2 ml	At least 50% improved at 1 year	Expensive, experimental	May contribute to muscle, nerve and fascia regeneration

ADR (common to all agents)

- Urinary retention
- UTI
- Transient haematuria
- De-novo storage LUTS
- Urethral prolapse
- Periurethral abscess
- VVF

DESMOPRESSIN
Arginine Vasopressin. V2 receptor analogue (collecting duct)
Minimal vasopressor effect. Also activated fVIII
Formulations
- Oral 0.1-0.4 mg/ day
- Nasal 10-40 ug/ day
- Oral lyophilised 0.5-1 mg/ day in men and 0.25 mg women (More effective oral form)

Used in nocturnal enuresis as first line therapy along with enuresis alarm

Short term improvement, does not cure enuresis

In women- OAB and men BPE complicate nocturia and appropriate additional therapy is beneficial
Registered for use in multiple sclerosis, also used in spinal injury
34% men and 46% women experience a >50% reduction in nocturia
Well tolerated. But not advisable >65 yrs. Women- Dose reduction to 0.25 mg per day

ADR: Hyponatremia (headache, nausea, vomiting, seizures, death). Especially if female, elderly, cardiac failure and high urine output

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Stone

1) Cystinuria

- Cystinuria is an inherited autosomal recessive disorder characterised by defect in intestinal and renal tubular transport of dibasic amino acids (Cystine, Ornithine, Lysine and Arginine – COLA). Even though high urinary concentrations of the all the four amino acids also exists; only Cystine leads to stone formation due to poor solubility.
- Cystine is a dimer composed of two cysteine molecules linked via disulfide bond. **Cystine is much less soluble than cysteine**.
- Cystinuria has varying incidence: 1 in 1000 to 1 in 17000, however it contributes to up to 10% paediatric stones.

Pathogenesis and genetics:

The main contributor to cystine crystallization is supersaturation because there is no specific inhibitor of cystine crystallization in the urine. Because of poor solubility precipitation and subsequent stone formation occur at physiologic urine conditions. The solubility is highly pH dependent (300mg/L, 400mg/L and 1000mg/L at pH 5, 7 and 9 respectively). Other factors like ionic strength and urinary macromolecules may influence cystine stone formation. Hypercalciuria, hyperuricosuria and hypocitraturia have been found in varying degress (up to 45%) with cystinuria and may contribute to stone formation and progression.

The current classification based on International Cystinuria Consortium (ICC) is based on chromosomal location of the genetic mutation. Two genes involved have been identified – SLC3A1 (on chromosome 2) and SL 7A9 (on chromosome 19). Homozygotes with either of the genetic mutations have higher urinary cystine concentrations and higher risk of stone formation, while hetrozygotes with Type B mutations have higher urine cystine levels though the risk of stone formation did not change.

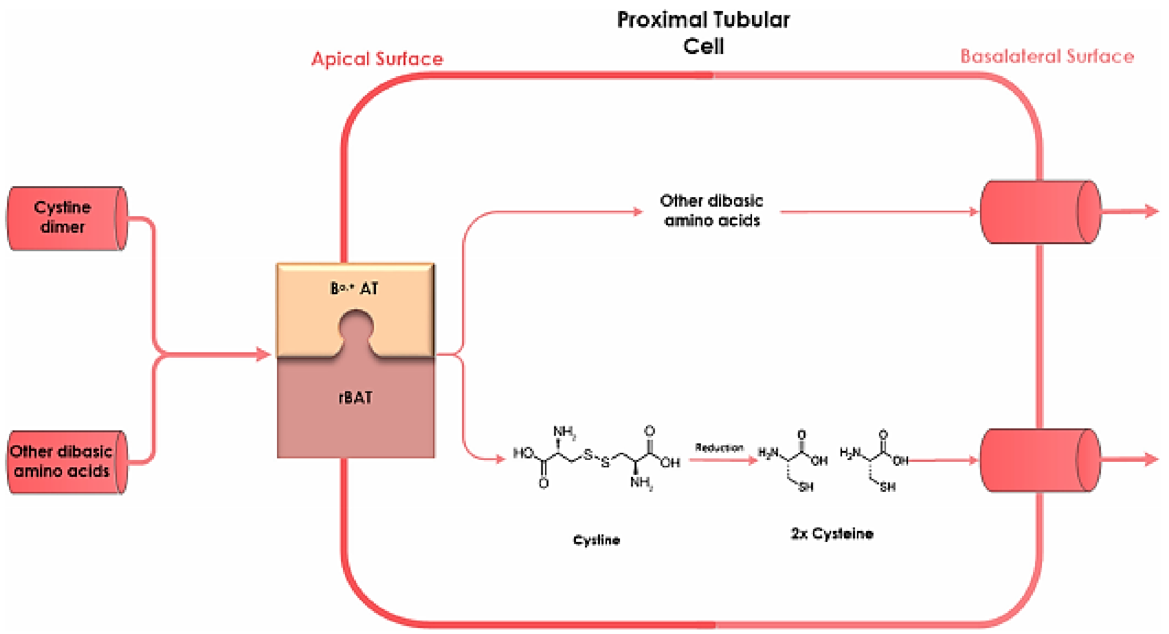


Figure 1. Transport of cystine and other dibasic amino acids in the proximal tubule. Normally, cystine is reabsorbed by the apical membrane of the proximal tubule by the transport system $b^{0,+}$. The transport system $b^{0,+}$ is a heterodimer composed of 2 subunits, the light subunit $b^{0,+}$ AT, which is encoded by the *SLC7A9* gene sequence, and the heavy subunit rBAT, which is encoded by the *SLC3A1* gene sequence. This transport system is affected in patients with cystinuria. Inside the cell, cystine is reduced to 2 molecules of cysteine, which exit the cell across the basolateral membrane. (Color version available online.)

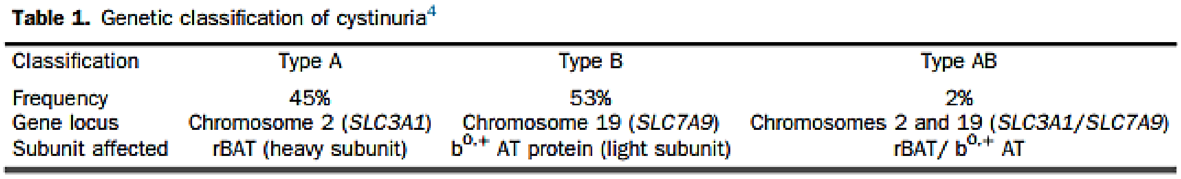


Table 1. Genetic classification of cystinuria[4]

Classification	Type A	Type B	Type AB
Frequency	45%	53%	2%
Gene locus	Chromosome 2 (*SLC3A1*)	Chromosome 19 (*SLC7A9*)	Chromosomes 2 and 19 (*SLC3A1/SLC7A9*)
Subunit affected	rBAT (heavy subunit)	$b^{0,+}$ AT protein (light subunit)	rBAT/ $b^{0,+}$ AT

Clinical features:

The clinically significant manifestations are related to stone formation and might include nausea, flank pain, hematuria, recurrent urinary tract infections, and rarely acute or chronic renal failure.

A high index of suspicion should be held in patients with family history of cystinuria or stone disease, recurrent crystalluria or stone formation in the first 2 decades of life.

Cystinuria should also be suspected in patients with large staghorn calculi filling the collecting system and requiring surgical management.

There is no pathologic correlation between the urinary excretion of the other dibasic amino acid ornithine, lysine, arginine.The gastrointestinal implications of impaired absorption of cystine have no clinical significance, because cystine absorption is maintained by the ability of the small intestine to absorb oligopeptides containing cystine, resulting in comparable serum levels with normal people.

Diagnosis:

In 2006, Dello Strologo and Rizzoni proposed a definition of cystinuria:

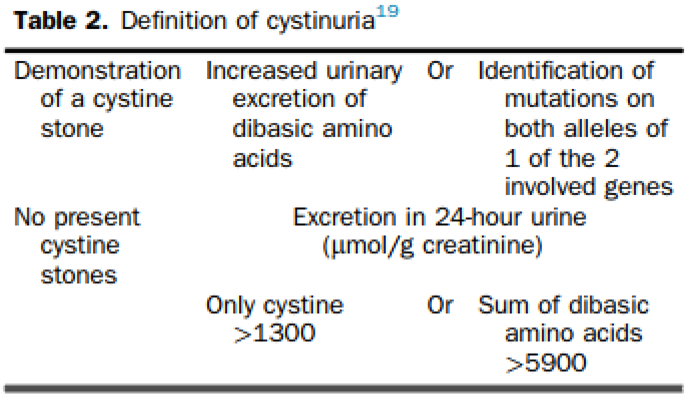


Table 2. Definition of cystinuria[19]

Demonstration of a cystine stone	Increased urinary excretion of dibasic amino acids	Or	Identification of mutations on both alleles of 1 of the 2 involved genes
No present cystine stones	Excretion in 24-hour urine (µmol/g creatinine)		
	Only cystine >1300	Or	Sum of dibasic amino acids >5900

Labarotory investigations

The initial test of choice is microscopic morning evaluation of the urine and might reveal the presence of the pathognomonic **hexagonal cystine crystal**s in up to 25% of patients with cystinuria. Because cystine is one of the sulfur-containing amino acids, the urine might have the characteristic odor of rotten eggs.

The **sodium-cyanide-nitroprusside test** offers a rapid **qualitative** determination of cystine concentration. Cyanide reduces cystine to cysteine, which then binds to nitroprusside, causing a red-purple color change in 2-10 minutes. This test detects cystine levels higher than 75 mg/g of creatinine. It is propagated as a cheap screening test for homozygotes, but is not specific.

A positive cyanide-nitroprusside test must be followed by an **ion-exchange chromatographic quantitative analysis of a 24-hour collected urine sample, to confirm the diagnosis**. The normal rate of cystine excretion is up to 30 mg/ day (= 0.13 mmol/day).

A stone composition analysis should also be performed. Cystine stones are **pale yellow and have a waxy appearance**. Electron microscopic evaluation coupled with x-ray diffraction crystallography has helped identifying components of the stones. Two subtypes of cystine calculi have been identified, smooth and rough. **Smooth calculi seem to be more resistant to extracorporeal shock wave lithotripsy (ESWL) fragmentation**. Pure cystine stones are observed in 60%-80% of cases, whereas in 20%-40% cystine is mixed with calcium oxalate, calcium phosphate, or magnesium ammonium calcium phosphate.

Imaging

On **plain radiography kidney, ureter, bladder** films, cystine stones **are radio-opaque** because of their disulfide bond and the presence of sulfur atoms, but **less radioopaque** than calcium stones, having **a ground glass or homogenous appearance**. Nevertheless, they might appear radio-opaque in cases of large staghorn or mixed stones.

Renal ultrasonography is an effective modality for detecting all types of urinary stones, and, because of its low cost and avoidance of radiation exposure, it can be used for following up new stone development, recurrence, and stone resolution over time, being used in combination with XRAY KUB.

Helical computed tomographic **(NCCT)** scan without intravenous contrast might be the test of choice in patients with high stone burdens. Cystine stones appear **poorly attenuated**, with CT-collimation and stone size influencing the attenuation and are distinguished as **rough or smooth, possibly predicting the success of ESWL.**

Treatment

Medical treatment and conservative measures:

The primary goal of the treatment is to prevent cystine stone formation by improving the solubility of urinary cystine. The treatment approaches include mainly **dietary measures, measures that decrease urinary cystine concentration and drugs leading to reduction of cystine to the more soluble cysteine**. Initial management methods should always include hydration and urinary alkalization. If the patient does not respond to this conservative approach, additional drugs, such as **D-penicillamine, alpha-MPG (mercaptopropionylglycine or tiopronin), and captopril** can be used.

1) **Hydration**: Fluid intake should reach at least 3 L/day in children and 4-5 L/day in adults, to preserve a urine volume of >2 L/1.73 m2 in children and >2.5 L/ day in adults. The individual rate of cystine excretion can be a guide to estimate the optimal urine output to achieve a urine concentration of <200-300 mg/L which is the solubility limit of cystine at urine pH of 7.
2) **Dietary modification**:
    a. Protein restriction and especially restriction of the intake of the **cystine's precursor methionine** is advocated. A high consumption of **animal protein** has been associated with an increase in urinary calcium excretion and a reduction of urinary pH and citrate excretion, metabolic changes that are considered as risk factors for stone formation. Methionine is abundant **in protein-rich food such as meat, fish, egg whites, cheese, soy, wheat, nuts, seeds, and beans.**
    b. **Decreased sodium intake -** a reduction of sodium chloride has shown to be able to decrease cystine excretion as much as 156 mg/day, and therefore a limitation of salt intake to **2 g/day** is recommended. This can be achieved by avoiding repeated salting and by the reduction of salty meals and fast food.
3) **Urinary alkalization**: The **solubility of cystine is greater with higher pH**. Therefore, an important approach to medical management of the disease is urinary alkalization using supplementation with an oral alkali. The first line-alkalizing agent is **nowadays potassium citrate.** The target urine pH between **7.0 and 7.5**. Very high urine alkalization should be avoided, as it might increase the **risk of calcium phosphate formation and predispose to urinary tract infections.**
4) **Pharmacologic treatment:** When conservative treatment measures, such as hydration and urine alkalization, are not sufficient, pharmacologic therapy with **cystine binding thiol** agents is applied. Thiol compounds contain sulfhydryl groups and work by reducing the disulfide bond, producing 2 molecules of **cysteine** combined with the thiol component of the drug, which are more soluble than the homodimer cystine.

a. **D-penicillamine**- Not frequently used presently because of adverse events such as nephrotic syndrome, dermatitis and pancytopenia.
b. **Alpha-Mercaptopropionylglycine** (Alpha-MPG/Tiopronin)-Better tolerated with lesser adverse events than D-penicillamine and therefore enjoys clinical superiority. The adverse events include rash, arthralgia, pemphigus, thrombocytopenia, polymyositis, proteinuria, and nephrotic syndrome. Tiopronin is also costlier than Dpenicillamine.
c. **Captopril** – Side effects include fatigue, hypotension and chronic cough (Like other ACE inhibitors). May be used in patients with concomitant hypertension.

Surgical treatment

Surgical management of cystine stones does not differ significantly from other urinary tract stones and depends on the size and location of the stone. Minimally invasive techniques are preferred compared with open surgical procedures and include mainly ESWL, retrograde ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL).

a) **ESWL** - Although cystine stones are considered to **be relatively resistant to ESWL**, the low invasiveness of the technique and the fact that cystinuric patients have recurrent stone events make ESWL an effective treatment modality and the primary therapy option for cystine stones of upper ureter and kidney stones less than 1.5cm. Multiple sessions may be required.
b) **URS** – for ureteric stones/RIRS for accessible and amenable pelvic/renal stones.
c) **PCNL** – For larger renal/upper ureteric stones and staghorn/complex stones. PCNL can also be combined with ESWL (sandwich therapy) for complex stones.
d) **Open surgery** – For larger stones/difficult anatomy open surgery – pyelolithotomy/ureterolithotomy may be needed. This may also be considered for simultaneous repair of anatomic abnormalities such as PUJO.

Even after surgery, the patient should be on conservative measures and be periodically monitored for recurrence, urine cystine levels (to modify conservative management) and to look for side effects of drug therapy.

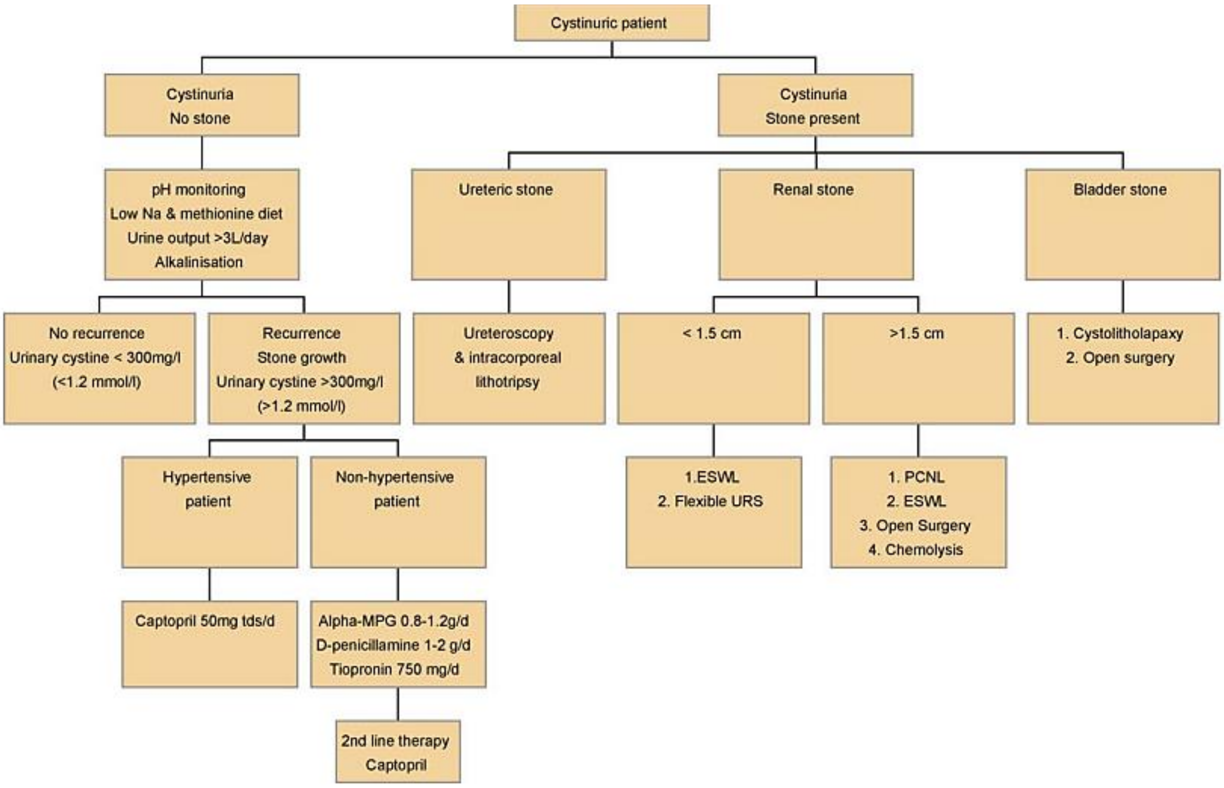


Fig. 1 – Algorithm for management of cystinuric patients. ESWL: extracorporeal shock wave lithotripsy, PCNL: percutaneous nephrolithotomy, URS: ureterorenoscopy.

2) Hyperoxalosis

- Oxalosis or calcium oxalate deposition in tissues occurs secondary to inherited disorders (**primary oxalosis/hyperoxaluria**); or secondary to other causes (**enteric/dietary**).
- Calcium oxalate deposits within renal tissue as nephrocalcinosis and also forms renal stones (nephrolithiasis). This leads to progressive renal injury and inflammation and tubular obstruction leading to interstitial fibrosis, declining renal function and eventually ESRD.
- When ESRD sets in with decline in GFR, calcium oxalate starts to deposit in **extra renal tissues** in a process called **systemic oxalosis**. Calcium oxalate deposits have been reported in the myocardium, cardiac conduction system, kidneys, bones and bone marrow. This leads to cardiomyopathy, heart block and other cardiac conduction defects, vascular disease, retinopathy, synovitis, oxalate osteopathy and anemia that are noted to be resistant to treatment.
- Hyperoxaluria is defined as urinary oxalate greater than **40mg/day**.

Primary hyperoxaluria:

This is a result of a rare autosomal recessive disorder in glyoxylate metabolism.

The primary enzyme catalyzing conversion of glyoxylate to glycine is **alanine/glyoxylate aminotransferase (AGT)** which is synthesized in the **liver**. Mutations in the gene synthesizing, leads to **primary hyperoxaluria type I (PH I)**. These patients have elevated oxalate and frequently glycolate.

Primary hyperoxaluria type 2 (**PH2**) is associated with defect **in glyoxylate reductase/hydroxypyruvate reductase (GRHPR)** in the liver resulting in hyperoxaluric nephrolithiasis, but with much **less aggressive course** with regard to renal failure than PH I. Unlike PH I, **GRHPR is not exclusive to liver**, it is also synthesized by various other tissues in the body. Hence in cases of ESRD needing renal replacement therapy, isolated kidney transplant may be undertaken. (cf: combined liver-kidney transplant may be required in PH 1).

A third type **non I, non II accounts for 5%** of primary hyperoxaluria clinically indistinguishable from the other two. Primary hyperoxaluria type 3 (**PH3**) is caused by a defective mitochondrial enzyme, 4-hydroxy-2-oxoglutarate aldolase (**HOGA**), which is thought to play a role in hydroxyproline metabolism. Although PH3 is associated with hyperoxaluria and severe hypercalciuria, the recurrent calcium oxalate stone formation seen in early childhood may become clinically silent later in life, and there are **no reports to date of progression to ESRD** in these patients.

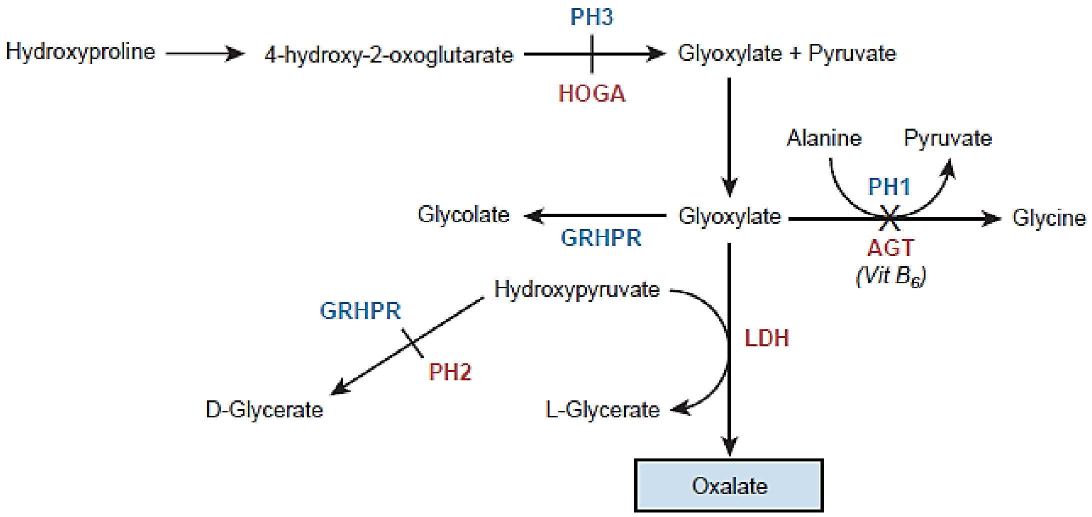


Figure 51-6. Pathway of oxalate metabolism in the liver. Defects in alanine:glyoxylate aminotransferase (AGT) are associated with primary hyperoxaluria type 1 (PH1), defects in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) are associated with primary hyperoxaluria type 2 (PH2), and defects in 4-hydroxy-2-oxoglutarate aldolase (HOGA) are associated with primary hyperoxaluria type 3 (PH3). LDH, lactate dehydrogenase.

If untreated, primary hyperoxaluria inevitably leads **to ESRD, which occurs by age 15 in 50% and associated with overall death rate of approximately 30%.**

As liver is the only organ (PH I) responsible for the detoxification of glyoxylate, **combined liver-kidney transplant** is the accepted treatment for most patients with severe primary hyperoxaluria.

Secondary hyperoxaluria

Enteric hyperoxaluria:

The most common cause of acquired hyperoxaluria is enteric hyperoxaluria. This is associated with chronic diarrheal states by which fat malabsorption results in saponification of fatty acids with divalent cations such as calcium and magnesium, and increasing pool of available oxalate for reabsorption.

Dehydration, hypokalemia, hypomagnesuria, hypocitraturia and low urine pH also increase the risk of oxalte stone formation in chronic diarrheal states.

Malabsorption of any cause can lead to increased intestinal oxalate absorption. This includes small bowel resection, intrinsic disease, jejunojejunal bypass, bariatric surgery and gastric bypass.

Dietary hyperoxaluria:

Increased intake of oxalate rich food such as nuts, chocolates, brewed tea, spinach, broccoli, strawberries and rhubarb can lead to hyperoxaluria. Increased animal protein intake can also lead to increased urinary levels of calcium and oxalate.

Ascorbic acid supplementation (Vitamin C) has shown to increase urinary oxalate levels by in vivo conversion to oxalate although increased clinical rates of stone formation have not been proven.

Oxalobacter formigenes, an oxalate degrading bacterium is a potential modulator in intestinal oxalate levels. Reduced levels or absent colonization was found in stone formers.

Cystic fibrosis patients, many of whom are exposed to prolonged antibiotic use, have decreases Oxalobacter levels and increased urinary oxalate.

Screening for hyperoxaluria:

Screening for hyperoxaluria must be undertaken in **every child with the first episode** of renal stone and **all adults who present with recurrent** calcium oxalate stones.

Screening should also be done at first presentation of **nephrocalcinosis or family history** of stone disease **at any age**. Furthermore, screening must be offered **to relatives of an index case**.

PH1 should be strongly considered in the differential in any patient with **renal failure of unknown etiology, particularly when there is nephrocalcinosis with reduced renal function or a high occurrence of renal stones**. Presence of **monohydrate calcium oxalate crystals in biological fluids or tissues** is also a strong pointer towards primary hyperoxaluria and should be followed up with additional testing.

Diagnosis:

Diagnosis of hyperoxaluria is established using a combination of clinical, radiological, biochemical, histopathological and genetic studies in primary hyperoxaluria.

In patients with a clinical suspicion for hyperoxaluria, the diagnostic workup should begin with ultrasound or other radiological imaging of the kidneys and the rest of the urinary tract to confirm the presence of nephrocalcinosis and urolithiasis.

Biochemical:

- **Stone analysis** should be done and may yield the initial diagnostic clues for PH. Stones in PH are composed of **monohydrate calcium oxalate (whewellite) which assumes a dumbbell shaped form**. In contrast in secondary hyperoxaluria the stone is usually composed of a combination of whewellite and weddelite.
- **24-hour urine oxalate levels** along with urinary glycolate and glycerate levels may aid in diagnosis of PH.
- In ESRD patients with low GFR, **plasma oxalate levels** help to confirm diagnosis of systemic oxalosis.
- Non-invasive, definitive diagnosis of PH is provided by testing of AGXT, GRHPR and HOGA1 **genes.**
- Other available diagnostic tests include use of **PCR in stool** samples to identify oxalobacter formigenes. Also, increased intestinal oxalate absorption can be assessed by an absorption test using **(^{13} C2)** oxalate.

Radiological:

a) Kidney – two distinct patterns
    a. **Medullary nephrocalcinosis**
    b. **Cortical nephrocalcinosis** – CT scan may be better to differentiate these.
b) CT scan may also identify oxalosis in other organs such as bowel wall, muscle and arteries.
c) Echocardiography may help in oxalosis of the heart.

Histopathological:

Skin biopsy may be necessary for skin lesions secondary to calcium oxalate deposition which can resemble the lesions of calciphylaxis. On histopathological examination, calcium oxalate crystals demonstrate a characteristic **birefringence** when examined under polarized light.

Treatment

Conservative measures:

1) **Hydration** to 3-4 litres/day. Special attention in fluid loss states like diarrhea and vomiting.
2) **Dietary modification** – especially in secondary dietary hyperoxaluria. Calcium intake should not be restricted as it complexes with oxalate and prevents its absorption. However, excessive intake of Vitamin C should be avoided.
3) **Pyridoxine** - Pyridoxine functions as a **cofactor** for the enzyme AGT which is defective in PH1. Administration of supraphysiological doses of pyridoxine may stabilize this enzyme and also enhance its enzymatic activity. The recommended initial dose of pyridoxine is 5 mg/kg with a maximum dose of 20 mg/kg. Pyridoxine has been demonstrated to be **effective in only 30% of the patients.** In patients in whom pyridoxine does work, early initiation may delay progression to ESRD.
4) **Urinary alkalization** - Alkalinization of the urine is well known to prevent stone formation as **citrate complexes with calcium and thus decreases the amount of calcium oxalate available for precipitation.** This same principle can be used in patients with hyperoxaluria.
5) **Probiotics** - Despite our knowledge of O. formigenes and its use of oxalate as an energy source, the use of probiotics to reduce urinary oxalate excretion has not been demonstrated in human studies. The results in animal studies however have been encouraging.

Surgery:

1) Surgery for stone includes ESWL, PCNL, URS or open procedures.
   ESWL may be mistakenly used on areas of nephrocalcinosis instead of stones due to lack of direct visual assessment which is achieved with endoscopy. Further, gravel in the urinary tract following the ESWL procedure may form a **nidus for calcium oxalate deposition** and recurrent stone formation in patients with hyperoxaluria.
2) **Renal replacement therapy**
    a. **Dialysis** - Oxalate deposition occurs when the oxalate levels reach the threshold for supersaturation which is estimated to be 30-45 µmol/L. Hemodialysis (HD) removes oxalate

more efficiently than peritoneal dialysis (PD). However, there is significant oxalate rebound following hemodialysis and levels can reach 80% of the pre-hemodialysis levels.

b. **Transplantation** - As the defective enzyme is liver specific in PH1, these patients require **preemptive liver, sequential liver- kidney, or combined liver-kidney transplantation**. Transplantation strategy is decided based on individual presentation and clinical course as disease expression may vary among patients with PH1. **Preemptive liver transplantation** can be considered in patients who have progressive renal disease and approach a GFR of 50 mL/min per 1.73 m2. **Sequential liver-kidney transplantation can be performed in children who are small for a combined liver-kidney transplant**. In contrast, **combined liver kidney transplant is best suited for patients who are on chronic renal replacement therapy and not responsive to pyridoxine**.

Isolated kidney transplantation may be the procedure of choice for adult patients who are sensitive to pyridoxine. However, in isolated renal transplant, allograft survival rates have been reported to be inferior in patients with primary hyperoxaluria compared to patients who received renal transplant for a non PH1 cause of ESRD.

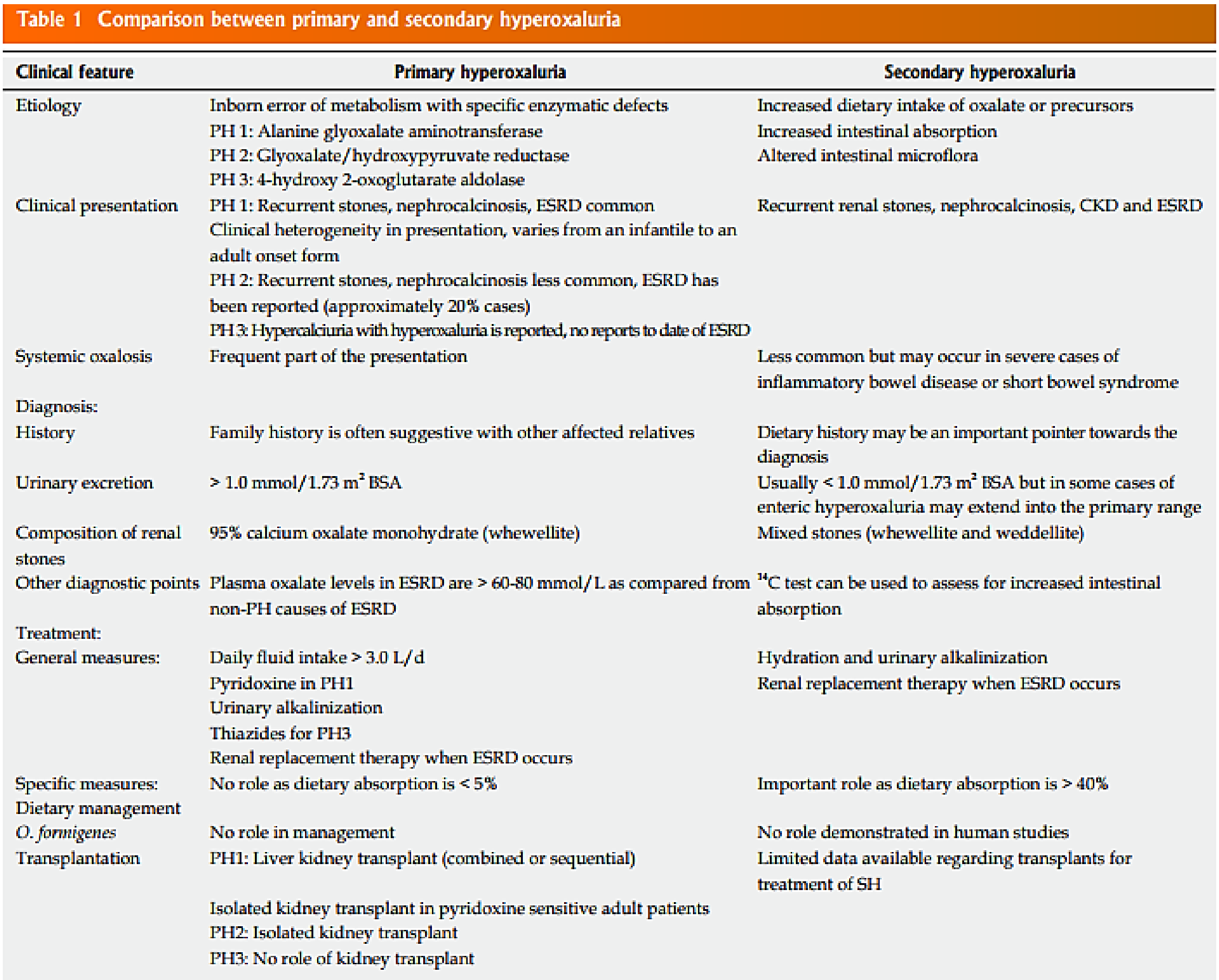


Table 1 Comparison between primary and secondary hyperoxaluria

Clinical feature	Primary hyperoxaluria	Secondary hyperoxaluria
Etiology	Inborn error of metabolism with specific enzymatic defects PH 1: Alanine glyoxalate aminotransferase PH 2: Glyoxalate/hydroxypyruvate reductase PH 3: 4-hydroxy 2-oxoglutarate aldolase	Increased dietary intake of oxalate or precursors Increased intestinal absorption Altered intestinal microflora
Clinical presentation	PH 1: Recurrent stones, nephrocalcinosis, ESRD common Clinical heterogeneity in presentation, varies from an infantile to an adult onset form PH 2: Recurrent stones, nephrocalcinosis less common, ESRD has been reported (approximately 20% cases) PH 3: Hypercalciuria with hyperoxaluria is reported, no reports to date of ESRD	Recurrent renal stones, nephrocalcinosis, CKD and ESRD
Systemic oxalosis	Frequent part of the presentation	Less common but may occur in severe cases of inflammatory bowel disease or short bowel syndrome
Diagnosis:		
History	Family history is often suggestive with other affected relatives	Dietary history may be an important pointer towards the diagnosis
Urinary excretion	> 1.0 mmol/1.73 m^2 BSA	Usually < 1.0 mmol/1.73 m^2 BSA but in some cases of enteric hyperoxaluria may extend into the primary range
Composition of renal stones	95% calcium oxalate monohydrate (whewellite)	Mixed stones (whewellite and weddellite)
Other diagnostic points	Plasma oxalate levels in ESRD are > 60-80 mmol/L as compared from non-PH causes of ESRD	^{14}C test can be used to assess for increased intestinal absorption
Treatment:		
General measures:	Daily fluid intake > 3.0 L/d Pyridoxine in PH1 Urinary alkalinization Thiazides for PH3 Renal replacement therapy when ESRD occurs	Hydration and urinary alkalinization Renal replacement therapy when ESRD occurs
Specific measures: Dietary management	No role as dietary absorption is < 5%	Important role as dietary absorption is > 40%
O. formigenes	No role in management	No role demonstrated in human studies
Transplantation	PH1: Liver kidney transplant (combined or sequential) Isolated kidney transplant in pyridoxine sensitive adult patients PH2: Isolated kidney transplant PH3: No role of kidney transplant	Limited data available regarding transplants for treatment of SH

3) Calyceal diverticulum

Calyceal diverticula are **non-secretory, transitional epithelium lined eventrations of the renal collecting system that are filled with urine**. A narrow neck communicating with collecting system is typically present, which permits the diverticulum to passively fill with urine.

They are an incidental finding in **0.2-0.6% of patients undergoing renal imaging**. Stone formation is seen in **9-45%** patients.There is no sex/side predilection. They are most commonly seen in the upper calyx >middle calyx>lower calyx.

Many theories have been proposed for their development including congenital (persistence of third and fourth generation ureteral bud branching in the embryo) and acquired: obstruction, achalasia around the the sphincters surrounding minor calyx, local cortical abscess and veiscoureteric refux.

Classification:

A) **Wulfsohn** :
   a. Type I – adjacent to upper or lower polar calyx (communicate with minor calyx/infundibulum). On IVU appears **bulbous with narrow infundibulum**.
   b. Type II – larger, central diverticula communicate with the renal pelvis/major calyx and tend to be symptomatic. On IVU, appears more **spherical with shorter necks**.

B) **Dretler**: Both anatomical and recommended treatment included
   a. Type I – Open mouth and short neck (ESWL)
   b. Type II – Closed mouth and short neck (URS)
   c. Type III – Closed mouth and long neck (PCNL)
   d. Type IV – Obliterated neck (PCNL)

Clinical features:

Many are picked up incidentally.

Hematuria, pain and UTI may be associated with stone formation.

Diagnosis:

Ultrasonography delineates a fluid filled area more centrally located near the collecting system than a simple renal cyst. When filled with microcalculi, USG characteristically demonstrates **layering effect** within the diverticulum – between clear fluid above and echo-dense debris without shadowing below.USG will image this milk of calcium within the diverticulum as the the patient changes position.

IVU/CT/MR urography demonstrates pooling **of contrast in the delayed** images. Cross sectional imaging can also delineate the precise anatomy.

Treatment:

Patients who are asymptomatic do not need treatment, but should be followed up periodically with ultrasound/cross sectional imaging

Treatment is required for stone and its complications such as pain/infection.

ESWL: Diverticulae with short wide neck may clear the stone with ESWL. However the overall stone free rate for ESWL is only around 21%.

URS/RIRS: May be used for diverticulae with short neck in the upper/middle calyx with stone size <2cm.

PCNL: This is the procedure of choice for calyceal diverticulum with stone – it provides the best chance to become stone and symptom free. Additionally ablation of the diverticular cavity and epithelium is possible through the percutaneous approach.

A direct percutaneous approach to the calyceal diveticulum allows use of rigid nephroscope for stone extraction, dilation and incision of the diverticular neck (if required).

Laparoscopy: Symptomatic calyceal diverticula with thin overlying renal parenchyma, large stone burden and anteriorly placed inaccessible diverticulae may be managed with laparoscopy (though rarely used).

4) Stents in Urology

(This answer refers to ureteral stents. For a general question not specifying, urethral stents may also be added. Please refer to Dr. Heman Prasad ES' BPH topic from HOSS bank for urethral stents – Non operative management of BPH)

Zimskind in 1967 was the first to describe cystoscopic placement of indwelling ureteral stents for obstructed ureters. Gibbons was the first to patent a barbed stent as a self retaining mechanism.

The first double-J or double pigtail stent was developed almost simultaneously by **Finney and Hepperlen in 1978**.

Stent technology:

The ideal stent is easy to insert, has the ability to relieve intraluminal and extraluminal obstruction, has excellent flow characteristics, is resistant to encrustation and infection, is chemically stable after implantation in the urinary environment, and does not induce patient symptoms.

Stents should therefore have **high tensile strength, a low friction coefficient, memory, self retainment mechanism, and should be biocompatible and affordable**.

Biomaterials:

I. **Non-metallic stents**
   a. **Silicone** – most biocompatible material tested to date but has a high friction co-efficient and flexibility make it difficult to navigate thorough tortuous or obstructed ureter.
   b. **Polyethylene** – Brittle, prone to encrustation, blockage and fragmentation hence no longer preferred
   c. **Polyurethrane** – Currently used stents commonly use polyurethrane
   d. Proprietary copolymers – **Silitek, C-flex** (can resist extrinsic compressive forces), **Percuflex, Tecoflex**

II. **Metallic stents**
   a. Self explanding metallic **Wallstent** - Failure rates high due to in growing hyperplastic tissue.
   b. **Resonance** metallic ureteral stent – Tightly coiled spirals of nickel-chromium-molybdenum alloy designed to resist encrustation and tissue in growth.
   c. Newer metal stents – **Silhouette** (less prone to kinking and can resist higher compressional forces), **Passage and Snake** stents (more flexibility)
   d. **Memokath 051** ureteral stent – made of nickel-titanium alloy (nitinol) with thermo-expandable anchoring mechanism.
   e. **Uventa** – Nitinol stent with segmental thermally expandable mechanism. Has PTFE coating to prevent tissue in growth
   f. **Allium** stent – Nitinol alloy, expandable mesh stent coated with biocompatible polymer to prevent stent in growth. Was specifically developed for use in distal ureter and has an intravesical anchor to facilitate removal.

A common problem for all metal mesh stents is the reduced long term patency due to migration, encrustation and erosion. Coatings to prevent hyperplasia and stent in groeth include paclitaxel eluting metal mesh stents (animal model) and zotarolimus eluting metal stent.

III. **Biodegradable stents:** Theoretically eliminate the need for cystoscopic removal and prevent occurrence of forgotten stents. All biodegradable stents are still experimental.
   a. High molecular weight polymers such as **polylactide or polyglycolide**. Surface modification of these with hydroxyethylmethylacrylate (HEMA) or acrylic acid results in improved biocompatibility and allows use in urinary environment.
   b. **Uriprene** – composed of L-glycolic acid, polyethylene glycol and barium sulphate. This achieved degradation after 4 weeks in animal models.
   c. **Magnesium yttrium alloy** –This alloy is biodegradable and inhibits bacterial activity.
   d. **Tissue engineered stents** – Studies are ongoing using chondrocytes on poly glycolic acid scaffold to create tissue engineered stents.

Coatings:

Drug eluting and anti-adhesive coatings are under investigation with the goal of improving handling, reducing biofilm formation, preventing encrustation and improving patient comfort.

1) **Hydrogel** – reduces friction and increases elasticity.
2) Pentosan polysulfate (**PPS**), phophorylcholine and polyvinylpyrrolidone (**PVP**) reduce inflammatory response, encrustation and biofilm formation.
3) **Diamond like carbon** (DLC) decrease friction and improves biocompatibility.
4) Silicone coated with **oxalobacter formigenes derived oxalate degrading enzymes** demonstrated reduced encrustation.
5) **Triclosan**-eluting stent (Triumph) decreased Proteus mirabilis growth in animal study and reduced stent pain and urinary symptoms.
6) **Ketorolac** eluting stent (Lexington) for reducing stent symptoms.
7) Sustained release varnish containing **chlorhexidine** (CHX-SRV) coated stents reduced bacterial growth in vitro.
8) **Antibiotic** coating stents including rifampin, tigecycline and clarithromycin coated stents are in preliminary phase of study.

Stent design:

1) **Grooved** stent – to have better extraluminal flow and total overall flow
2) **Spirastent** – helical metal ridges to improve urine flow
3) **Open-Pass ureteral** stent – radially expanding baskets along the length to trap fragments of stone after ESWL. Entrapped fragments are removed at time of stent removal.
4) **Double-helix spiral stent** – absence of intravesical coil decreased reflux.
5) **Tail stents or buoy stents** – Size tapers towards bladder end to a distal tail rather than a coil. These have shown better drainage, reduced bladder inflammation and reduced irritative symptoms.
6) **Dual durometer stents** – Conventional upper body and softer biomaterial in the lower part to decrease bladder symptoms
7) **Magnetip stent** – it has metallic head in the distal end and can be removed with a magnetic tipped urethral catheter.

Indications for stenting:

Most commonly performed to relieve obstruction – intrinsic (stone, tumors or strictures) or extrinsic (tumor, vessels, retroperitoneal fibrosis or lymphadenopathies). The relief of obstruction can be temporary or permanent.

Absolute and usually emergent indications:

1) Drainage of bilateral obstruction
2) Obstruction in a solitary kidney/contralateral renal dysfunction
3) Obstruction with sepses
4) Intractable renal colic may also be an emergent indication

Other indications:

1) **ESWL** – Pre-ESWL stenting is not mandatory unless solitary kidney or increased stone bulk
2) **URS** – Post URSL stenting is done for sizeable residual fragments, solitary kidney, bleeding or perforation, UTI and balloon dilated ureteric orifice (with trauma/edema). DJ stenting may be placed for 1-2 weeks after initial unsuccessful URSL before a secondary URSL.
3) **PCNL** – Residual stone burden, perforation of collecting system, extensive edema, risk of hydrothorax, concomitant PUJ narrowing.
4) **Reconstructive surgery** – Pyeloplasty, ureteric reimplantation, ureteric trauma, renal transplantation.
5) Before gynaecological/urological/abdominal surgery – **to identify ureters** intraop.
6) In treatment of malignant upper tract urothelial carcinoma – **to induce reflux** for BCG administration.

Technique:

DJ stenting can be done under combined cystoscopic and fluoroscopic guidance, fluoroscopy only guidance or cystoscopic and ultrasound guidance (in pregnant women).

Complications:

1) **Stent symptoms** – Storage LUTS, hematuria, flank pain. Sexual dysfunction also reported in some.
   Irritation of bladder mucosa especially trigone by the distal portion of the stent, reflux of urine and smooth muscle spasm are thought to contribute.
   Positioning upper coil in the upper pole and avoiding the lower coil to cross midline have been shown to decrease stent symptoms.
   Alpha blockers may mitigate stent symptoms. Solifenacin and tamsulosin have been shown to be beneficial.
2) **Stent migration**
3) **Urinary tract infection** – Antibiotics recommended only in symptomatic UTI, no role for long term prophylaxis
4) **Encrustation** – duration of indwelling time most important factor. Timely exchange especially in high risk groups like pregnancy, UTI, metabolic or congenital anomalies recommended.
5) **Forgotten or neglected stents**.

5) Flexible ureteroscopy/ureteric access sheath

Flexible ureteroscopy

Flexible ureteroscopy and improvement in flexible scope technologies have had one of the greatest impacts on changing endourology.

Components:

The fundamental components of flexible ureteroscopes include the **optical system, deflection mechanism and the working channel.**

1) Non-digital optical system

The non digital optical system consists of flexible fibreoptic image and light bundles. Improvements in image bundle construction have allowed closer packing of more fibres, resulting in inproved images, smaller outer diameters, and larger working channels.

2) *Deflection mechanism*

The deflection mechanism is one of the integral parts of the flexible ureteroscope. It allows complete maneuverability within the intrarenal collecting system. When the tip moves in the same direction as the lever, it is said to be "**intuitive**". The plane of deflection is designated by the reticle, seen as a notch within the field of view of the ureteroscope. The active deflection mechanism wears out with time and improvements in construction aim to increase durability. Most current flexible ureteroscopes permit deflection to **180 degrees or more** (180-275 degrees).

Active deflection occurs only at the distal tip of the ureteroscope and the deflected tip may not be long enough to access lower pole calyx. Most flexible ureterosopes have a more flexible segment of the scope just proximal to the active deflection due to the weakness in the durometer of the sheath. This **secondary passive** deflection helps to reach lower pole. Newer scopes have a **secondary active deflection and exaggerated deflection** to address lower pole access.

3) *Working channel*

All currently available flexible ureteroscopes have working channels of 3.6 Fr diameter allowing use of instruments up to 3 Fr while still permitting adequate irrigation.

Digital flexible ureteroscopes:

The transition from flexible to digital scopes was possible to advancement in charged coupled device (**CCD**) and complementary metal oxide semi-conductor sensors (**CMOS**). The CCD is mounted on the tip of the scope (***chip on the stick scope***).

Advantages of digital scopes:

1) Eliminates need for internal optics, potentially making scopes more durable.
2) Eliminated several parts of the system – separate camera, separate light cord and light source.
3) Steps such as white balancing and focussing avoided.
4) Without fibre-optic bundles in the shaft, the size of the working channels can be increased.
5) Image size is larger and much clearer. No honeycombing/pixellation (Moire effect).
6) The above can decrease operating time and efficiency of the surgery.

Disadvantages:

1) Larger tip diameter (most are around 8Fr now) may prevent passage through narrow areas (VUJ, stricture, infundibulum). May need presenting, balloon dilation or ureteric access sheath.
2) Expensive – but the overall cost/efficacy gained by durability may make it cost effective.

Indications for flexible ureteroscopy:

Similar to any URS:

1) Treatment of urolithiasis
2) Treatment and surveillance of upper tract TCC.
3) PUJO or ureteral stricture treatment.
4) Evaluation of hematuria.
5) Removal of foreign body – migrated stent, suture, balloon catheters, fractured instruments.

Complications:

1) Perforation
2) Stricture
3) Submucosal/lost stone
4) Ureteric avulsion

Care and sterilization:

Laser fibre should not be introduced inside when the tip is deflected. Laser should not be fired inside the working channel; the tip has to be out and under vision. The Laser firing should not be too close to the tip either.

Flexible ureteroscopes, including the working channel, should be cleansed with warm water and non abrasive detergent after each use. Sterilization can be performed by gas (**ethylene oxide**), by soaking in **glutraldehyde solution** or by **STERIS system** (provides automated washing and rinsing in peracetic acid solution).

Ureteral acces sheath:

To facilitate access to upper tract that **requires multiple passages** (large stone burden/tumor/strictures) the ureteric access sheath was introduced.

In the pre-ureteric access sheath era this was achieved by multiple passes, two guidewires (working though which each time the scope had to be backroaded and safery wire). The procedure was more **traumatic, time consuming, cumbersome and compromised on the surgical outcome**. Also, the vision was poorer because of lesser place for irrigation to flow and increased resistance by the coapting ureter on the sides of the scope. The decreased vision further compromised safety and outcome.

To overcome these shortcomings **Takayasu and Aso in 1974** introduced a Teflon “guide tube”. Later, the technology was improved (lubricated outer coating, well tapered transition between inner obturator and outer sheath, and thin walls of the access sheath itself permitting larger lumen for better flow and visualisation) by **Ralph Clayman** in association with **Applied Sciences** to create the ureteral access sheath in its current form.

Parts:

1) Inner obturator
2) Outer cannula (sheath)
3) Locking mechanism – to keep obturator and outer sheath as one unit

The ureteral access sheath is available in sizes from 9Fr to 16Fr and lengths from 20cm to 55cm. The numbers on the access sheath – Eg: 12Fr/14Fr/35 – denote the size of the obturator, outer sheath and length respectively.

The choice of sheath depends on the gender, the postion and type of pathology and length of the ureteroscope to be used.

Procedure:

The inner obturator and outer access sheaths have hydrophilic coatings and have to be flushed separately before starting.

Under fluoroscopic guidance and over a guidewire the ureteric access sheath is advanced to the site of interst/upper ureter for RIRS. The obturator protrudes little beyond the inner sheath and this has to be factored in the right positioning of the outer sheath before removal of the guidewire. In case of resistance to passage, gentle pressure or waiting for the ureteric peristalsis to pass will allow the access sheath. In rare cases when the access sheath cannot be advanced, URS to pass the area of narrowing and passive/active dilation may be needed.

Advantages:

1) Pressure flow relationship:
    a. Decreases intrarenal pressure which permits increasing irrigation pressure. This along with better clearance of fragments improves vision.
    b. Decreases risk of sepsis.
    c. In malignancy, theoretically decreases risk of dissemination to bloodstream and spread to other parts of exposed ureteric/bladder mucosa.
2) Allows repeated passages – makes procedure less traumatic, expedious and efficient
3) Prevent buckling of the ureteroscope in the bladder
4) Overall efficiency of the procedure and cost better – time, success and morbidity
5) Preserves ureteroscope wear and tear
6) Other uses:
    a. DJ stenting may be done over the access sheath under fluoroscopic guidance
    b. In PCNL, ureteral access sheath may decrease intrarenal pressure for large stones and anticipated complex, long procedures. Also combination of retrograde and antegrade procedure can be done for large, complex stones to achieve better stone clearance.

Disadvantages:

1) Ureteral ischemia – larger access sheaths used for longer time have been proposed to decrease ureteral blood supply and predispose to ischemia. No conclusive evidence for the same.
2) Ureteral injury – mucosa trauma, perforation, avulsion.
3) Ureteral stricture formation
4) Technical - Depending on various makes – Kinking of the access sheath after removal of the obturator/buckling at the ureteric orifice

6) Intrarenal vascular anatomy and surgical implication in percutaneous renal surgery

Although the renal arterial anatomy is variable, in general the **main renal artery** divides into an **anterior** and a **posterior** branch.

The anterior segmental then divides **within or before the renal sinus** into four anterior segmental arteries: the **apical** and **lower** segmental arteries (which supply the tip of the upper pole and the entire lower pole, respectively), and the **upper and middle segmental arteries** (which supply the remainder of the anterior half of the kidney).

The posterior branch of the renal artery continues as **the posterior segmental artery** supplies the remainder of the posterior half of the kidney.

After the anterior segmental arteries and the posterior branch of the renal artery enter the renal parenchyma, they divide into:

- **interlobar** arteries, which are also **called infundibular arteries** owing to their course adjacent to the calyceal infundibula of the renal collecting system.
- At the corticomedullary junction, near the base of the renal pyramids, each interlobar artery usually divides into **two arcuate arteries** that run along the renal pyramid.

- The next division is into the **interlobular arteries**, which run along the outer surface of the renal pyramids and are derived at **right angles from the arcuate arteries**.
- The final divisions, the **afferent arterioles** of the glomeruli, come off the interlobular arteries in the peripheral renal cortex. Each renal arteriole is an "**end-artery**," meaning that each cell in the kidney derives its blood supply from one arteriole.

Since the arterial supply ends in an end artery, renal arterial vascular injury must be avoided to prevent loss of renal function.

The potential for arterial injury is least in the **Brödel line, which is an avascular plane approximately at the lateral margin of the kidney**, extending from the superior apex of the kidney (limited by the circulation of the apical anterior segmental artery) to the lower pole of the kidney (limited by the circulation of the lower anterior segmental artery).

The **venous anatomy** of the kidney does not have the same defined structure as the arteries. Moreover, there is **free cross circulation** among the intrarenal veins via arcades. This enhances vascular outflow from the kidneys, reduces the risk of venous congestion, and makes renal venous injury less damaging to renal function than arterial injury.

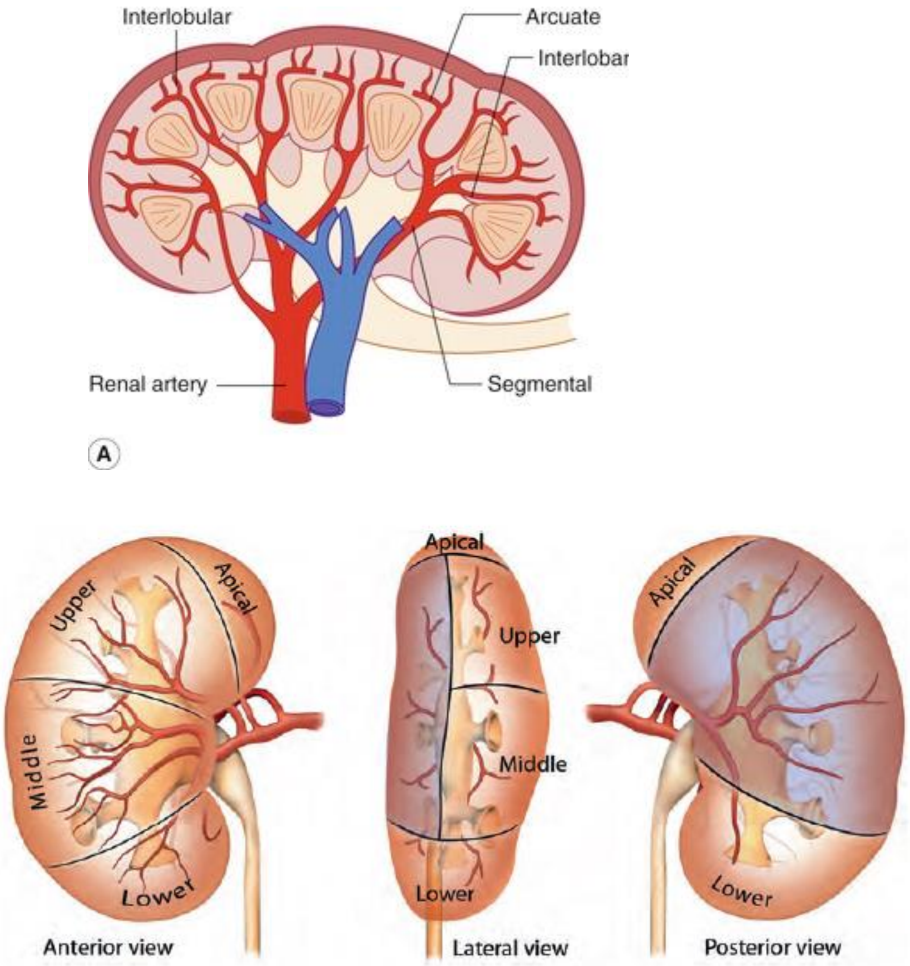


Figure 8-7. Arterial supply to the kidney. The kidney is supplied by the anterior and posterior branches of the main renal artery. The anterior branch supplies both the anterior half of the kidney and the polar regions via four segmental branches. The posterior branch of the renal artery supplies the posterior aspect of the kidney (represented by the shaded region). An avascular plane, known as Brödel line, separates the anterior and posterior circulations.

One of the most significant complications with percutaneous intrarenal access is vascular injury which may lead to hemorrhage with hypotension, loss of functioning renal parenchyma, and arteriovenous fistula or pseudoaneurysm.

Through their **3D polyester resin corrosion endocasts** obtained from fresh cadavers, **Sampaio et al** compared punctures at various sites in the collecting system to determine safest point of entry into the collecting system with minimal vascular injury.

1) Intrarenal access through **the infundibulum**
    a. At superior pole – Is dangerous because this region is surrounded by large vessels. Infundibular arteries and veins course parallel to the anterior and posterior aspects. In their series they found a **67%** chance of vascular injury with upper infundibular puncture (**26% of which were arterial**). The most serious accident is the puncture of **the posterior segmental** artery which was related to the infundibulum in 57% endocasts. An injury to the posterior segmental artery may result in significant loss of renal parenchymal function (up to 50%) as well as significant hemorrhage.
    b. Middle kidney – Chance of arterial injury at interpole infundibulum **was 23%.** The middle branch of the posterior segmental artery was injured frequently.
    c. Lower pole – In 38% infundibular artery was found at the site of puncture and arterial injury was associated with **13% punctures** through lower pole infundibulum.

Additionaly, puncture at infundibulum **risks through and through puncture** and increases risk of injury to anterior segmental vessels which may be difficult to control with tube tamponade.

2) Intrarenal access through **renal pelvis** – there is high risk of injury to the posterior segmental vessel and hence should not be performed.
3) Intrarenal access through **calyceal fornix** – Puncture through fornix of calyx lead to venous injury in fewer than **8%** kidneys. There were **no arterial injuries** through forniceal puncture at any of the poles in their series.

Thus safest place to access percutaneously the collecting system is **directly into the calyceal fornix**, because this will avoid the interlobar (infundibular) arteries adjacent to the calyceal infundibula and the arcuate arteries that skirt the renal pyramid.

Vascular anatomy of ureteropelvic junction for endopyelotomy:

If there is a confirmed crossing vessel causing the PUJO, open/lap pyeloplasty with transposition of the vessel should be done than endopyelotomy because of risk of injury to the crossing vessel which may supply a significant area of the renal parenchyma.

For percutaneous endopyelotomy in cases without the crossing vessel, the **non vascular area at the PUJO is directly on the lateral wall** at the stenotic segment. Giving the incision posterolateraly, anterolateraly or medialy; risks injury to the segmental vessels.

7) A) Bio-effects of ESWL. B) Mechanism of action of ESWL. C) Optimizing outcomes of ESWL. D) Complications of ESWL

Mechanism of action of ESWL:

Stone break occurs due to direct mechanical stress of the incident shockwave and indirect effect of collapse of cavitation bubbles. These events occur simultaneously or separately at the surface of the stone and within the interior of the stone.

1) **Spall fracture** – Microcracks coalese together to cause spallation. Larger, spherical stones break by this mechanism.

2) **Squeezing-splitting/circumferential compression** – This occurs because of the difference in the sound speed between stone and the surrounding fluid. Current generation lithotripters in which F2 is very small do not work by this mechanism.
3) **Shear stress** – Transverse waves generated perpendicular to the incident wave. Stones such as calcium oxalate with alternating mineral and matrix induce shear waves.
4) **Superfocussing** – Amplification of stresses inside the stone due to geometry of that stone.
5) **Cavitation** – Cavitation bubble formed releases shockwave in the absence of boundaries or produces a cavitation microjet in the presence of boundaries that can accelerate to large speeds to produce stone break.
6) **Dynamic fatigue** – Accumulation of damage over the course of treatment leading to eventual stone destruction.

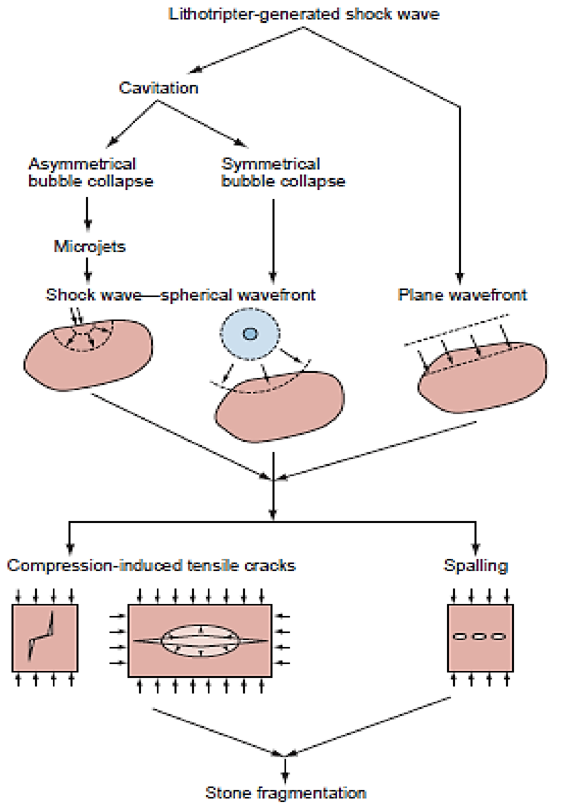

Lithotripter-generated shock wave
Cavitation
Asymmetrical bubble collapse
Symmetrical bubble collapse
Microjets
Shock wave—spherical wavefront
Plane wavefront
Compression-induced tensile cracks
Spalling
Stone fragmentation

Figure 54-11. **Summary of how the various mechanical forces generated by a lithotripsy shock wave might cause a kidney stone to fracture. (Reproduced with permission from Dr. Bradley Sturtevant.)**

Bioeffects/Complications of ESWL:

Acute extrarenal:

Though the potential for extrarenal complications exist, these occur rarely in clinical practice.

ESWL has been associated with trauma to liver, skeletal muscle (evidence by elevated bilirubin, LDH, CPK). But these fall to by 3-7 days and fall to normal by 3 months.

Visceral injuries – Perforation of colon, hepatic hematoma, splenic rupture, pneumothorax, urinothorax, pancreatitis (some association with diabetes mellitus also – no conclusive evidence) and abdominal wall abscess

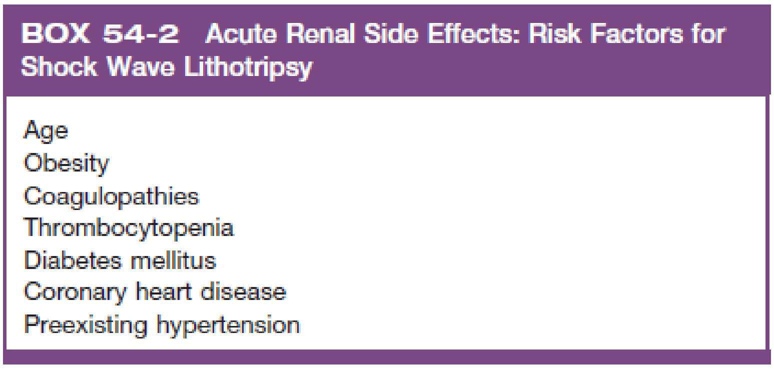
Extrarenal vascular complications – Rupture of hepatic artery, rupture of abdominal aorta, iliac vein thrombosis.

Cardiac arrhythmias were seen with Dornier HM3 (gating – synchronization with ECG was used). But this complication is not seen with newer generation non-water lithotripters.

There have been no long term effects on testes or ovaries; there is no association between ESWL and fertility. Pregnancy is however an absolute contraindication for ESWL.

Acute renal injury – both structural and functional:

1) Hematuria due to rupture of blood vessels (all sized vessels from glomerular to arcuate and interlobar affected) and tubular damage
2) Hematoma formation – Newer lithotripters with smaller, high intensity F2 have higher chance of subcapsular hematoma (3-12%). Preexisting uncontrolled hypertension had the highest risk of hematoma formation.
3) Loss of functional renal volume



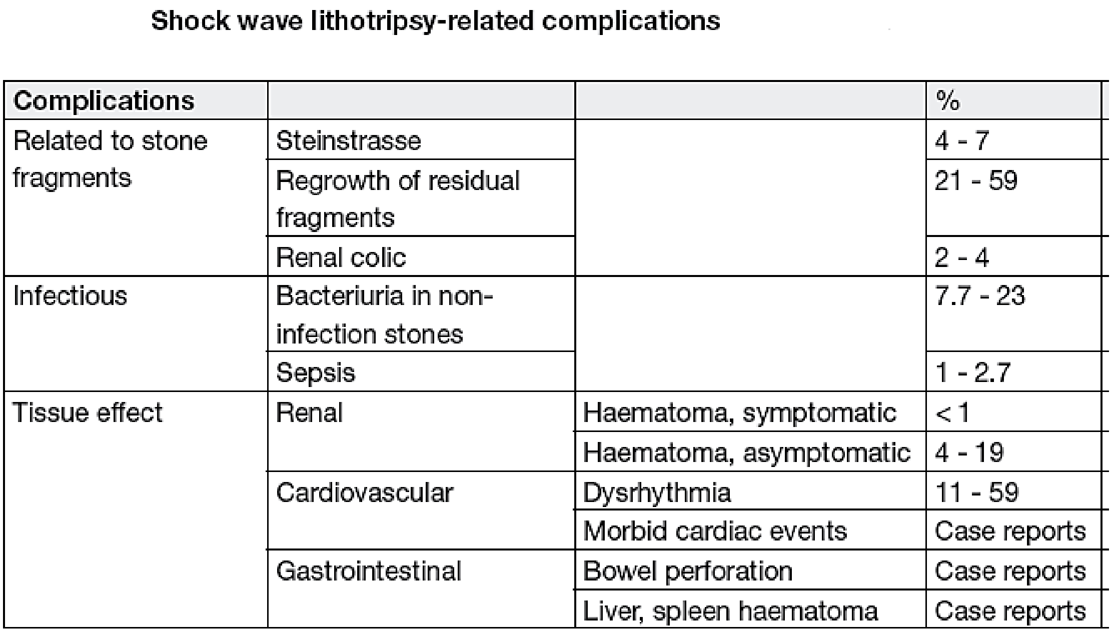
BOX 54-2 Acute Renal Side Effects: Risk Factors for Shock Wave Lithotripsy

Age
Obesity
Coagulopathies
Thrombocytopenia
Diabetes mellitus
Coronary heart disease
Preexisting hypertension

Chronic renal injury: both structural and functional changes:

All chronic changes are due to progress of acute renal injury at F2 to renal scar formation.

1) Hypertension
2) Decrease in renal function – significant decrease in effective renal plasma flow after 20 months of ESWL observed
3) Stone recurrence – May be higher in ESWL due to residual stone debris
4) Increase in incidence of brushite stones (may be due to loss of normal local urinary pH secondary to microvessels and collecting duct damage) Complications related to the procedure:
1) UTI/fever/sepsis
2) Acute colic due to passage of fragement
3) Urinary obstruction – may need intervention
4) Residual fragments/Failure – need for secondary procedure



Shock wave lithotripsy-related complications

Complications			%
Related to stone fragments	Steinstrasse		4 - 7
	Regrowth of residual fragments		21 - 59
	Renal colic		2 - 4
Infectious	Bacteriuria in non-infection stones		7.7 - 23
	Sepsis		1 - 2.7
Tissue effect	Renal	Haematoma, symptomatic	< 1
		Haematoma, asymptomatic	4 - 19
	Cardiovascular	Dysrhythmia	11 - 59
		Morbid cardiac events	Case reports
	Gastrointestinal	Bowel perforation	Case reports
		Liver, spleen haematoma	Case reports

Optimizing outcomes of ESWL:

1) **Patient and stone characteristics**: Stone >900 HUs and skin stone distance >9cm have lesser success rates with ESWL. Obese patients have lower success rates.
   Lower pole stone – Single dependent calyx, infundibulopelvic angle <70 degrees, infundibulum width <5mm diameter<4mm, length >3cm and infundibular length: width ratio >7 are poor predictors of success.
   So these groups of patients may be offered alternate forms of treatment.
   Pre-stenting especially with large stone burden and in solitary kidney scenario has shown to improve stone clearance.
   Antibiotics in sterile urine setting have no additional role as once thought however if there is obstruction/foreign body (stent)/proven urine C/s positivity antibiotics should be given.
2) **Adequate analgesia** – If not being done under GA, adeaquate analgesia permits lesser movement, better patient tolerance and better results.
3) **General anaesthesia** has shown to produce better results due to more control on movements.
4) **Slow frequency (rate) of shocks** – improves fragmentation and decreases renal damage.
5) **Ramping** – Beginning the treatment with lower energy followed by gradual increase in energy decreases renal damage by causing vasoconstriction. The initial low energy also causes less pain and improves patient compliance. Some have advocated a three minute pause between the ramping, however no recommendation.
6) **Acoustic coupling** – the coupling medium should be of low viscosity with sufficient quantity without any air bubbles. Direct application as a mound without squeezing from a tube allows uniform spread and prevents air bubble formation.
7) **Patient positioning** – For upper ureteric stones, few studies have shown supine position to be superior to prone. Similarly semilateral position has been tried for upper ureteric stones permitting higher energy shock delivery.
8) **Monitoring** of the stone during procedure and adjusting focal point to account for patient movements and breathing.
9) Post procedure **tamsulosin** has increased stone clearance rates with lesser pain events especially for stone >10mm
10) Other medications like calcium channel blockers, mannitol, Vit E and citrate (antioxidants) have been studied to decrease free radical induced injury with no conclusive benefit.
11) Percussion, Inversion and Diuresis (**PDI**) for lower pole stones – Mechanical or manual percussion in 45-70 degree Trendelenburg position following 500ml oral fluids with or without diuretics, or intravenous fluids has shown increased clearance of lower pole stones.
    However PDI should be used with caution in obese, CVA, GERD and those with pre existing back problems.

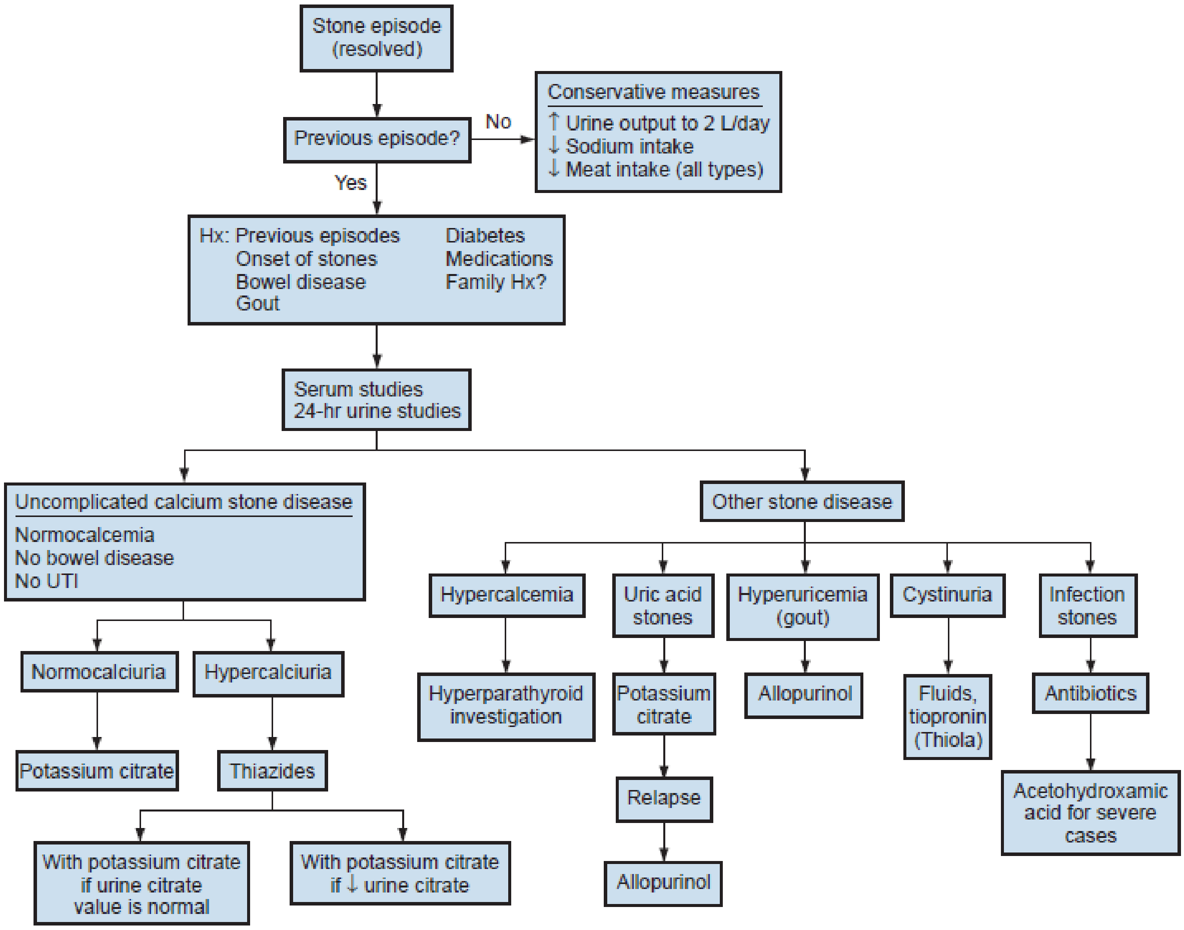
7) Evaluation of recurrent stone former and management according to report

A detailed history regarding prior stone episodes, medication history, diabetes, bowel disease, gout and family history should be obtained.
Recurrent stone formers need complete metabolic evaluation.

The investigations include:

1) **Blood investigations**:
    a. Complete blood count
    b. Basic metabolic panel (sodium, potassium, chloride, serum creatinine, blood urea nitrogen, CO2)
    c. Serum PTH
    d. Serum calcium and albumin
    e. Serum uric acid
2) **Urine investigations**:
    a. 24 hr urine -Total volume and urine pH
    b. 24hr urine – calcium
    c. 24 hr urine – oxalate
    d. 24 hr urine – citrate
    e. 24 hr urine –uric acid
3) Whenever possible **stone analysis** should be done: stone compostion can direct further metabolic work up or obviate further studies.
4) Imaging – NCCT is the preferred imaging modality. Functional study may be obtained before intervention.

The further evaluation depends on the metabolic work up as follows (simplified algorithm):



The general preventive measures to be followed with all urolithiasis are as follows:

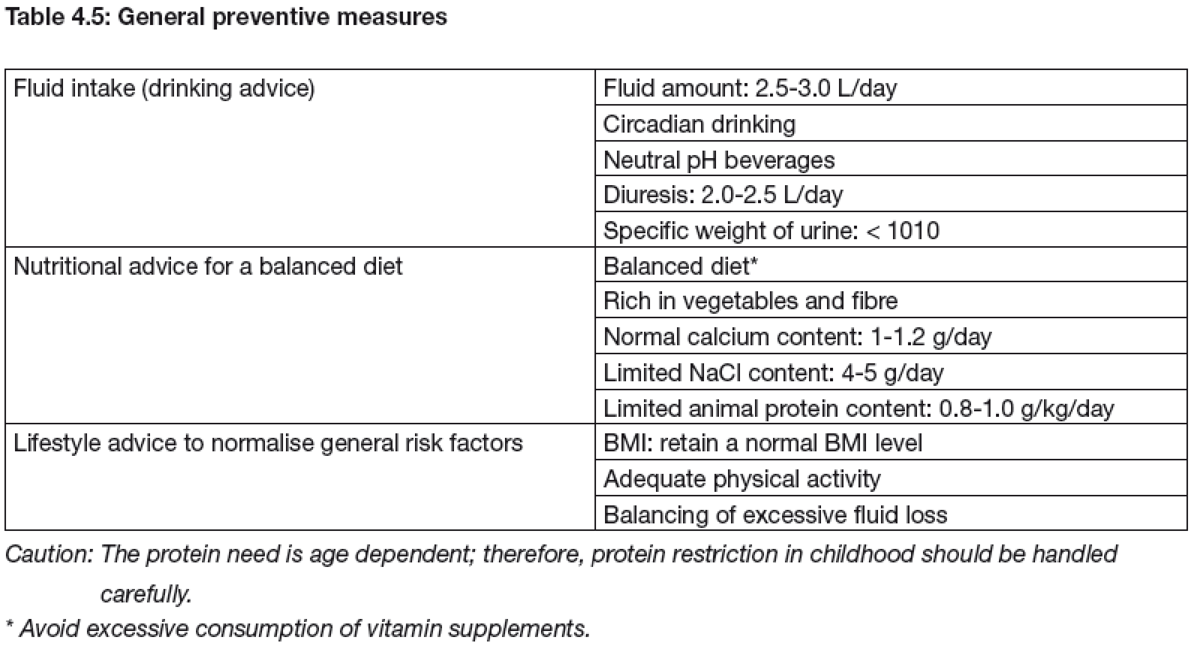


Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Circadian drinking
	Neutral pH beverages
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1010
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1-1.2 g/day
	Limited NaCl content: 4-5 g/day
	Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss

Caution: The protein need is age dependent; therefore, protein restriction in childhood should be handled carefully.

** Avoid excessive consumption of vitamin supplements.*

The various medications available for specific stones are as follows:

Agent	Rationale	Dose	Specifics and side effects	Stone type
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic	Calcium oxalate
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate
Thiazide (Hydrochlorothiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia.	Calcium oxalate Calcium phosphate
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine

Transplantation/Renovascular disease

*1. Perfusion fluids in renal transplantation

Kidney preservation

Mechanism of cell injury:

- Warm ischemic injury is due to failure of oxidative phosphorylation and cell death due to adenosine triphosphate (ATP) depletion
- ATP is required for the cellular sodium-potassium pump to maintain a high intracellular concentration of potassium and a low internal concentration of sodium.
- When the sodium-potassium pump is impaired, sodium chloride and water passively diffuse into the cells, resulting in cellular swelling and the "no-reflow" phenomenon after renal revascularization
- Cellular potassium and magnesium are lost, calcium is gained, anaerobic glycolysis and acidosis occur, and lysosomal enzymes are activated.
- This results in cell death.
- During reperfusion, hypoxanthine, a product of ATP degradation, is oxidized to xanthine with the formation of free radical scavengers that cause further cell damage.

Principle of simple cold storage of Kidneys:

Cellular energy requirements are significantly reduced by hypothermia.

This is done by surface cooling, hypothermic pulsatile perfusion, or flushing with an ice cold solution followed by cold storage.

If the electrolyte composition of the flush solution is nearly the same as that inside the cell, electrolyte balance will be maintained.

The basic methods of kidney preservation

- Pulsatile machine perfusion with a protein-based solution
- Hypothermic flushing followed by simple cold storage

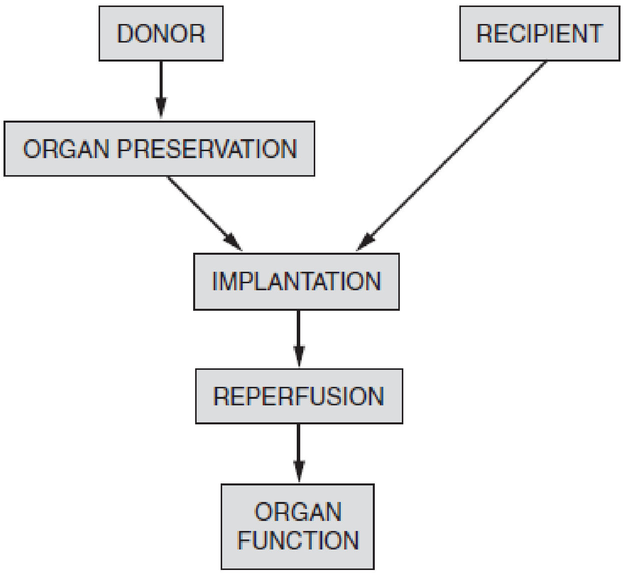


Figure 9–1 The transplantation cascade.

- Removal of the kidney from the circulatory system leads to disruption of the blood supply. The absence of oxygen delivery to the cells rapidly leads to major metabolic problems.
- Suppression of metabolism is essential to prolong the time of ischemia the kidney can sustain. Reducing the core temperature of the kidney to less than 4ºC results in a reduction of metabolism to 5% to 8% in most cells and diminishes enzyme activity.
- With a preservation solution, however, cold ischemia times can be significantly prolonged, and preservation quality can be improved—the solution effect

1. EuroCollins solution was a simple and cheap, intracellular-like preservation solution. Phosphate was used for pH buffering, and glucose served as the osmotic agent.

2. University of Wisconsin Solution

- Metabolic inert substrates such as lactobionate and raffinose served as osmotic agents. HES was used as a colloid.
- Scavengers (glutathione, allopurinol) and an ATP precursor (adenosine) were added to the solution. To date, UW-CSS is considered the "gold standard" preservation solution for kidney, liver, pancreas, and small bowel.

3. Histidine-Tryptophan-Ketoglutarate Solution

- HTK solution was initially introduced as a cardioplegic solution in open heart
- The solution consists of a very potent buffer, histidine, combined with two amino acids Tryptophan serves as membrane stabilizer and antioxidant, whereas ketoglutarate acts as substrate for anaerobic metabolism during preservation.
- HTK solution has a low viscosity, and to achieve complete tissue equilibration high volumes (approximately 15 L) have to be rinsed through the organs at low flow rates.

4. Colloids and Impermeants

- Glucose is a monosaccharide and was used in early cold storage solutions (e.g., EuroCollins).
- Because glucose is able to pass the cell membrane, it is a source for ATP and lactate in an anaerobic environment, reducing its impermeant effectiveness.
- Mannitol is a slightly larger monosaccharide, but is not metabolizable and does not pass the cell membrane easily. It is added for its beneficial effect as a radical oxygen scavenger to HTK solution. The largest and most effective saccharide is raffinose, which is used in UW-CSS.

5. Others-

Celsior

Clear to slightly yellow, sterile, non-pyrogenic solution for hypothermic flushing and storage of hearts. The solution is slightly acidic (approximate pH 7.3 at 20°C), slightly hypertonic (approximate calculated osmolarity 320-360 mOsmol/L) with low viscosity (1.15 cSt), and has a high buffering capacity (acidic approximately 11 mmol, alkaline approximately 7 mmol).

Perfadex – Lungs

2. Pathophysiology of renovascular hypertension and management

Definition of RVH- WHO :

- systolic >160 mm Hg or diastolic >95 mm Hg or both.
- The renal arterial lesion must be functionally significant (i.e., it must reduce blood flow by an amount sufficient to activate renin release, initiating RVH), relieved by correction of the offending lesion or removal of the kidney.

- 1-3% of all HTN
- 7% ,>65 age :- renal artery disease
- 25% , with CAD : - renal artery disease
- 50% , with pvd : - renal artery disease
- 3-6% of normotensive potential kidney donor :- renal artery disease

(1) the two-kidney hypertension model
where one renal artery is clipped and the other renal artery is left unaltered (2K1C)
(2) the one-kidney hypertension model
where one renal artery is clipped and the contralateral kidney is removed (1K1C).

- Because of the ischemia induced by the stenosis, renin secretion is increased from the juxtaglomerular apparatus of the ischemic kidney and suppressed in the normal contralateral kidney.
- As a consequence of the activation of the renin-angiotensin-aldosterone system (RAAS) and an increased production of angiotensin II (AII), there is peripheral vasoconstriction and hypertension.
- The key finding is that the hypertension that ensues is mediated by a vasoconstrictor, AII, and is therefore referred to as the **vasoconstrictor hypertensive model**.
- The normal contralateral kidney with its renin secretion suppressed and under a higher perfusion pressure is able to excrete most of the excess salt and water. Because there is limited sodium retention, there is no significant feedback inhibition of renin secretion in the stenotic kidney. Thus it continues to secrete AII and the vasoconstriction and hypertension is maintained.

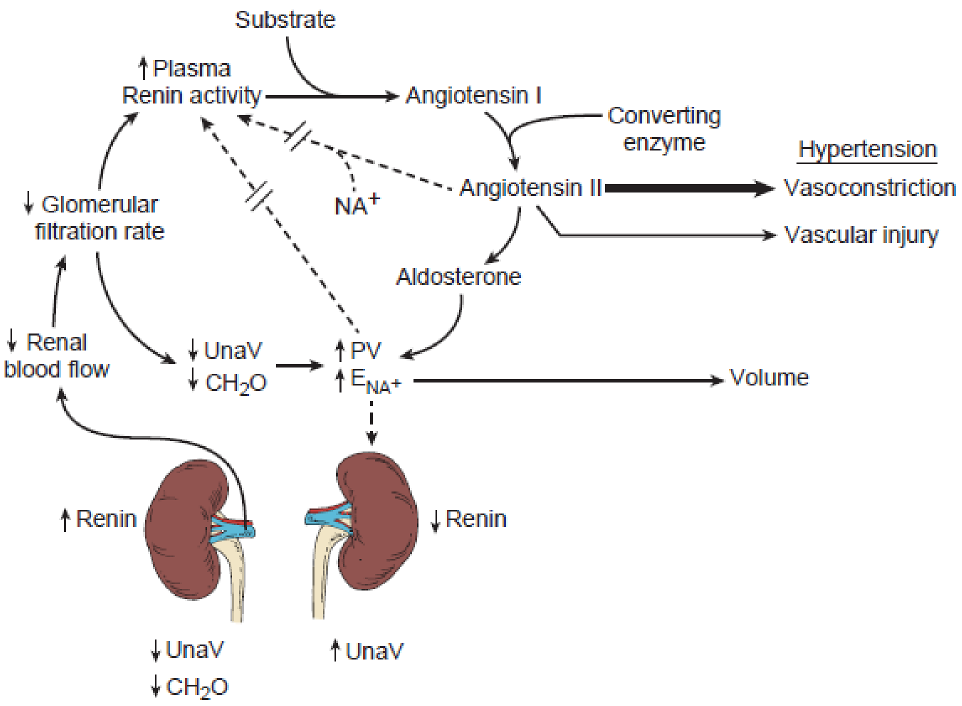


Figure 45-1. The renin system in the setting of unilateral renal artery stenosis with a normal contralateral kidney characterized by (1) high peripheral plasma renin activity, (2) contralateral suppression of renin release, and (3) a decrease in ipsilateral renal blood flow (RBF). The resultant hypertension is mediated by angiotensin II induced vasoconstriction. (From Vaughan E,

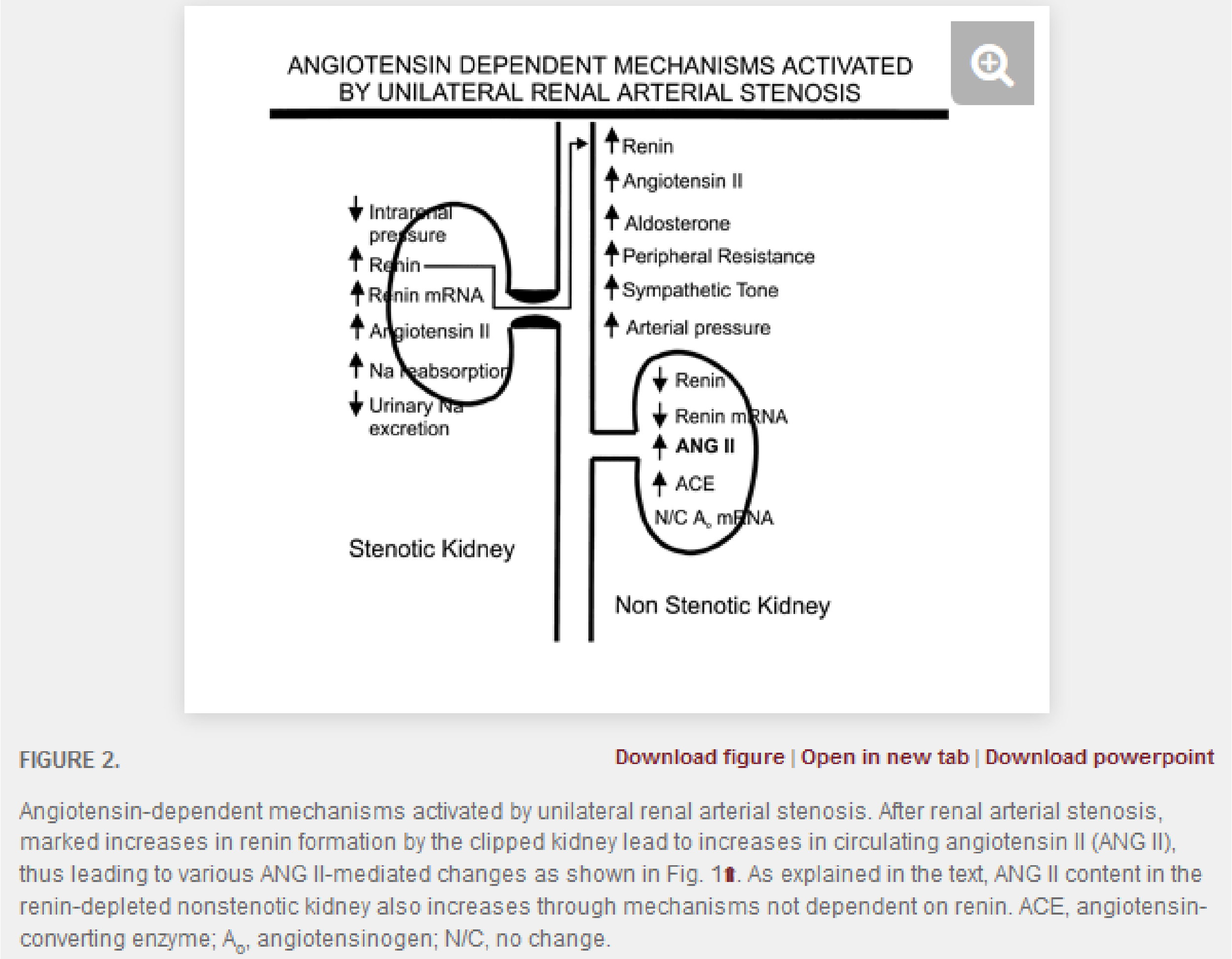


FIGURE 2.

Angiotensin-dependent mechanisms activated by unilateral renal arterial stenosis. After renal arterial stenosis, marked increases in renin formation by the clipped kidney lead to increases in circulating angiotensin II (ANG II), thus leading to various ANG II-mediated changes as shown in Fig. 1. As explained in the text, ANG II content in the renin-depleted nonstenotic kidney also increases through mechanisms not dependent on renin. ACE, angiotensin-converting enzyme; A_0, angiotensinogen; N/C, no change.

In RVH, apart from HTN, the entire renal functioning parenchyma is affected and causes ischemic nephropathy (def: decrease in the glomerular filtration rate (GFR) with several histologic changes like scarring, fibrosis, and tubular damage)
The degree of stenosis necessary to produce a reduction in RBF greater than
40% is ~70% to 80%, referred to as a "critical stenosis."

The poststenotic renal parenchyma demonstrates -

- vascular sclerosis
- cholesterol crystals
- tubular atrophy
- interstitial fibrosis with inflammatory cells
- atubular glomeruli
- focal or global glomerulosclerosis

Eddy classified progressive renal fibrosis into

1. cellular activation and injury phase
2. fibrogenic signaling phase
3. fibrogenic phase
4. destructive phase

3. Pathophysiology of rejection and recent advances in immunosuppression (essay)

Kidney transplant rejection can be classified by temporal occurrence of graft loss.

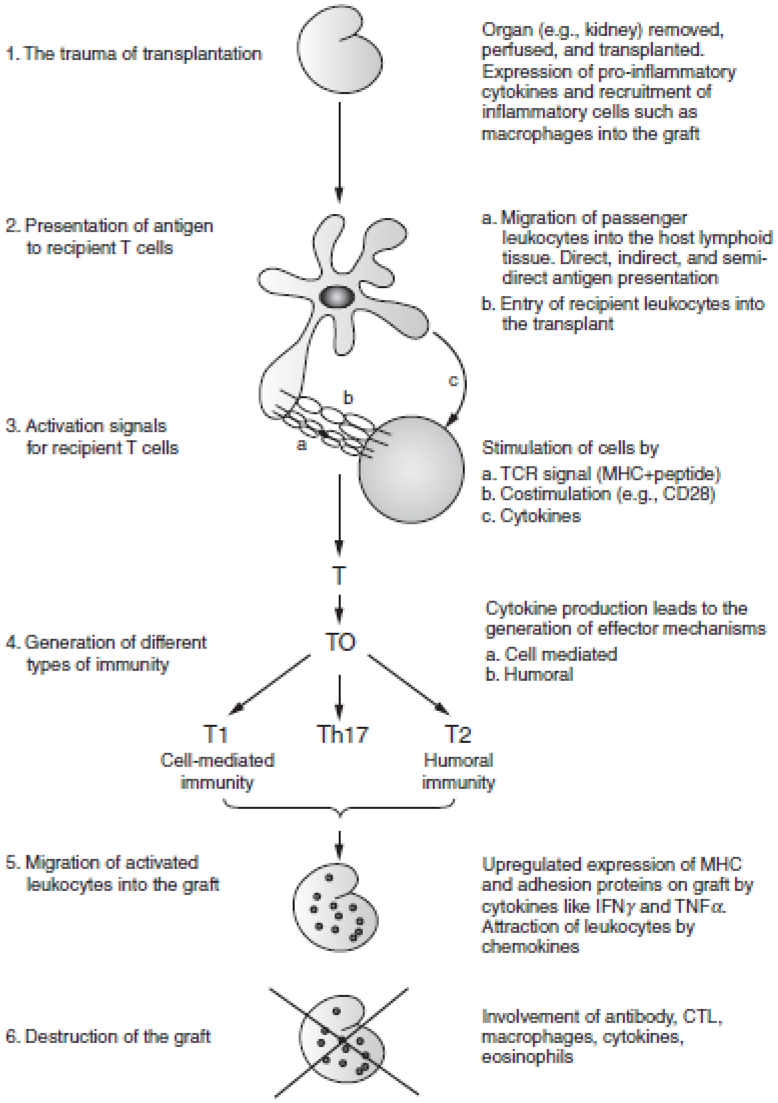

1. The trauma of transplantation
Organ (e.g., kidney) removed, perfused, and transplanted. Expression of pro-inflammatory cytokines and recruitment of inflammatory cells such as macrophages into the graft
2. Presentation of antigen to recipient T cells
a. Migration of passenger leukocytes into the host lymphoid tissue. Direct, indirect, and semi-direct antigen presentation
b. Entry of recipient leukocytes into the transplant
c
b
a
3. Activation signals for recipient T cells
Stimulation of cells by
a. TCR signal (MHC+peptide)
b. Costimulation (e.g., CD28)
c. Cytokines
T
TO
4. Generation of different types of immunity
Cytokine production leads to the generation of effector mechanisms
a. Cell mediated
b. Humoral
T1
Cell-mediated immunity
Th17
T2
Humoral immunity
5. Migration of activated leukocytes into the graft
Upregulated expression of MHC and adhesion proteins on graft by cytokines like IFNγ and TNFα. Attraction of leukocytes by chemokines
6. Destruction of the graft
Involvement of antibody, CTL, macrophages, cytokines, eosinophils

Figure 2–1 The evolution of the immune response after kidney transplantation. CTL, cytotoxic T cell; IFN, interferon; MHC, major histocompatibility complex; TCR, T cell receptor; TNF, tumor necrosis factor.

Hyperacute rejection occurs shortly after the reperfusion of kidney transplants. Recipient cytotoxic antibodies and complement react with donor vascular endothelial antigens, leading to a rapid activation of the coagulation cascade and graft thrombosis. This type of “humoral” rejection is rarely seen clinically today because of sensitive crossmatch tests to detect DSA.

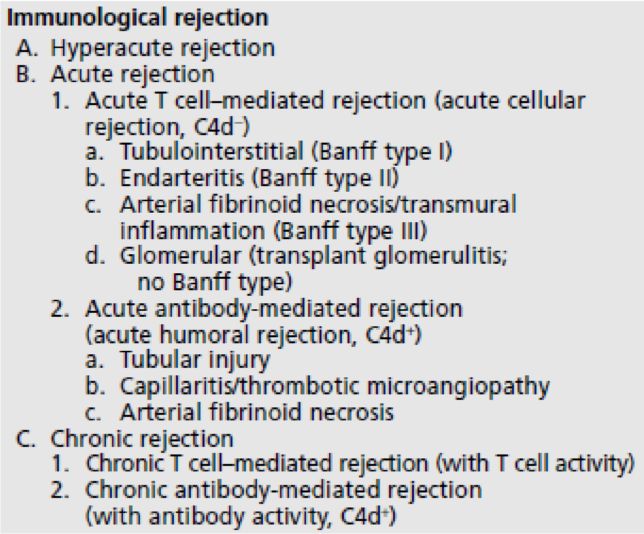
Accelerated Rejection Superimposed on ATN

- Accelerated acute rejection refers to rejection episodes occurring between days 2 and 5 post-transplant.
- Pre-transplant sensitization of the recipient to donor alloantigens is thought to be the cause. This arises from previous transplantation or, less commonly, blood transfusion.
- Accelerated acute rejection may be superimposed on ischemic ATN in which case there may be no signs of rejection or it may occur in an initially functioning allograft.
- The classic finding on renal bx is necrotizing arteritis: “fibrinoid” necrosis and inflammation of the arterial wall

Acute rejection

- classically occurs approximately 5 days after an allogeneic organ transplant without immunosuppression. Current immunosuppression protocols have reduced the rate of biopsy proved acute cellular rejection to 10% to 15% in the first year.
- MC sign is increasing serum creatinine and decreasing urine output.
- Symptoms may include pain, swelling over the graft, malaise, and fever; but these are rare.
- Urinalysis may show proteinuria, hematuria, or pyuria.
- Imaging studies may demonstrate decreased cortical blood flow and tubular function.
- Needle biopsy of the kidney graft is the current standard diagnostic test. The deposition of complement fragments (C4d) in peritubular capillaries is diagnostic of rejection associated with donor-specific antibodies.

Chronic rejection is characterized by a gradual deterioration of kidney function.
The histologic features of interstitial fibrosis, arteriolar sclerosis, and tubular atrophy rarely improve with augmented immunosuppression, and are in some cases the result of drug toxicity.



Immunological rejection

A. Hyperacute rejection
B. Acute rejection
  1. Acute T cell–mediated rejection (acute cellular rejection, C4d$^-$)
    a. Tubulointerstitial (Banff type I)
    b. Endarteritis (Banff type II)
    c. Arterial fibrinoid necrosis/transmural inflammation (Banff type III)
    d. Glomerular (transplant glomerulitis; no Banff type)
  2. Acute antibody-mediated rejection (acute humoral rejection, C4d$^+$)
    a. Tubular injury
    b. Capillaritis/thrombotic microangiopathy
    c. Arterial fibrinoid necrosis
C. Chronic rejection
  1. Chronic T cell–mediated rejection (with T cell activity)
  2. Chronic antibody-mediated rejection (with antibody activity, C4d$^+$)

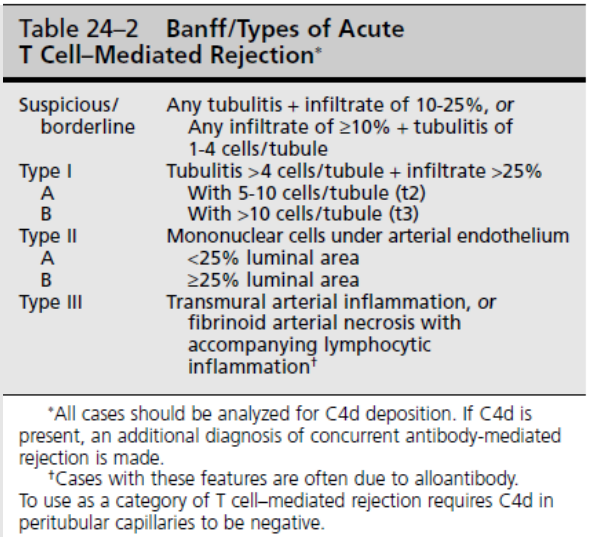


Table 24–2 **Banff/Types of Acute T Cell–Mediated Rejection**[*]

Suspicious/ borderline	Any tubulitis + infiltrate of 10-25%, *or* Any infiltrate of ≥10% + tubulitis of 1-4 cells/tubule
Type I	Tubulitis >4 cells/tubule + infiltrate >25%
A	With 5-10 cells/tubule (t2)
B	With >10 cells/tubule (t3)
Type II	Mononuclear cells under arterial endothelium
A	<25% luminal area
B	≥25% luminal area
Type III	Transmural arterial inflammation, or fibrinoid arterial necrosis with accompanying lymphocytic inflammation[†]

[*] All cases should be analyzed for C4d deposition. If C4d is present, an additional diagnosis of concurrent antibody-mediated rejection is made.

[†] Cases with these features are often due to alloantibody. To use as a category of T cell–mediated rejection requires C4d in peritubular capillaries to be negative.

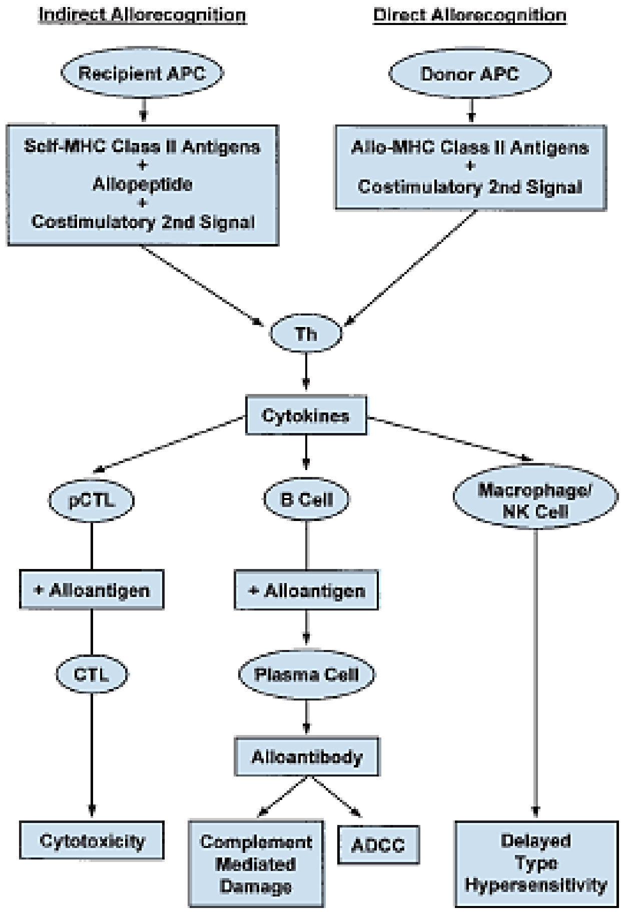


Figure 47-11. Cellular interactions in renal transplant rejection. CD4+ helper T cells (Th) are activated by antigen-presenting cells (APCs) that express incompatible major histocompatibility complex (MHC) class II antigens and provide a costimulatory second signal. The Th cells produce lymphokines that promote proliferation of B cells, maturation of CD8+ cytotoxic T lymphocytes (CTLs), activation of macrophages and natural killer (NK) cells, and induction of MHC class II antigens on renal cells. ADCC, antibody-dependent cell-mediated cytotoxicity; pCTL, precursor cytotoxic T cell.

Recent advances in immunosuppression are-

Some basics-

immunosuppressive agents can be classified into **three categories:**

induction agents-

- polyclonal antibodies (antithymocyte globulins)
- IL-2 receptor antagonists (basiliximab).

maintenance therapy-

- calcineurin inhibitors (cyclosporine and tacrolimus),
- mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus),
- antiproliferative agents (azathioprine and mycophenolic acid)
- corticosteroids

treatment for rejection-

- plasmapheresis
- intravenous immunoglobulin
- rituximab

Novel immunosuppressive agents –

Belatacept -

- a costimulation blocker for use in kidney transplantation. It is a selective T-cell blocker.
- It is a human fusion protein of cytotoxic T-cell antigen 4 (CTLA-4) and human IgG1.
- clinical trials comparing belatacept with cyclosporine suggest that they have similar efficacy, but belatacept preserves renal graft structure and function, and is associated with lower rates of chronic allograft nephropathy.
- The **initial dose** is 10 mg/kg on days 1 (before the intervention), 5, 14, and 28, and after weeks 8 and 12 following the transplantation.
- In the **maintenance phase** dose is 5 mg/kg every 4 weeks (3 days), starting at the end of the 16th week following the transplant.
- In trials such as BENEFIT and BENEFIT-EXT, the incidence of new-onset diabetes after transplantation (NODAT) with belatacept has been lower than that in patients treated with calcineurin inhibitors, and belatacept has shown a better cardiovascular and metabolic profile than currently used immunosuppressants.

Voclosporin

a cyclosporine analog.

PROMISE trial of low-risk renal transplant recipients with immediate allograft function compared low , medium, and high doses of voclosporin with tacrolimus in combination with a standard immunosuppressive regimen (anti-CD25 antibody, MMF, and corticosteroids).

Rejection rates were noninferior to tacrolimus and renal function was similar at 6 months after transplantation.

Prolonged release tacrolimus

Prolonged- release tacrolimus has a noninferior efficacy profile compared with convenient daily dosing, which is expected to improve patient compliance

Anti-CD40 monoclonal antibody

A fully human anti-CD40 monoclonal antibody, ASKP1240, has shown promise in phase 1 studies and that the antibody was safe and well tolerated

Treatment of antibody-mediated rejection

Bortezomib

- used for the treatment of acute antibody-mediated rejection
- The associated toxicity to be low, most commonly anemia or peripheral neuropathy.
- Dosing of bortezomib is 1.3 mg/m^2 on days 1, 4, 8, and 11.
- No adjustments are necessary for renal impairment

Eculizumab

- humanized monoclonal IgG antibody that binds to complement protein C5 and blocks the activation of the terminal complement.
- Eculizumab 600 mg weekly for six doses with plasmapheresis has also been successful in reversing refractory, early (mean time 6.5 days), acute antibody- mediated rejection in four transplant recipients.

4. Vascular access for CKD

The autologous arteriovenous (AV) fistula was introduced by Brescia and Cimino in 1966.

Temporary Vascular Access and Venous Catheters for Long-Term Use

Temporary Vascular Access-

- The preferred site for insertion is the right internal jugular vein because this provides the most direct route to the superior vena cava (SVC) and right atrium.
- The tip of the catheter should be placed at the junction of the SVC and the right atrium.

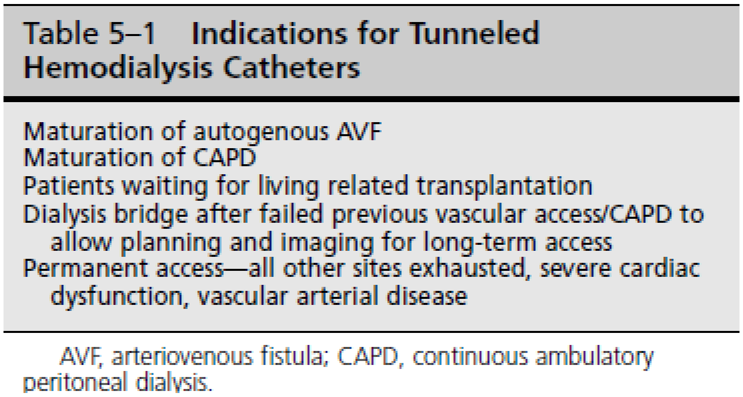


Table 5–1 Indications for Tunneled Hemodialysis Catheters
Maturation of autogenous AVF
Maturation of CAPD
Patients waiting for living related transplantation
Dialysis bridge after failed previous vascular access/CAPD to allow planning and imaging for long-term access
Permanent access—all other sites exhausted, severe cardiac dysfunction, vascular arterial disease

AVF, arteriovenous fistula; CAPD, continuous ambulatory peritoneal dialysis.

Modern cuffed, tunneled hemodialysis catheters, made of silicone or polyurethane – common catheters in use are dual-lumen catheters (Permacath, Quinton Instrument Co, Bothell, Wash; Vascath, Bard, Salt.

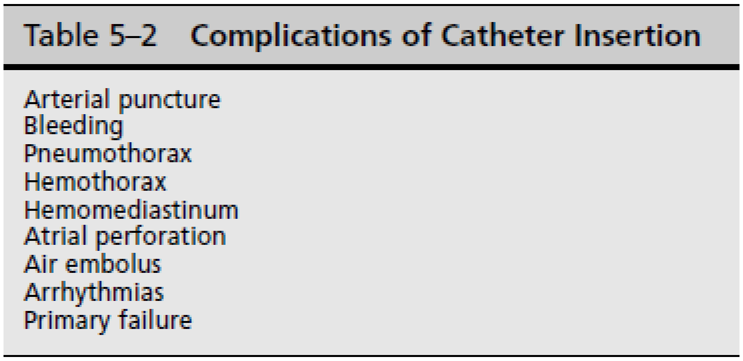


Table 5–2 Complications of Catheter Insertion
Arterial puncture
Bleeding
Pneumothorax
Hemothorax
Hemomediastinum
Atrial perforation
Air embolus
Arrhythmias
Primary failure

FISTULAS AND SYNTHETIC GRAFTS-

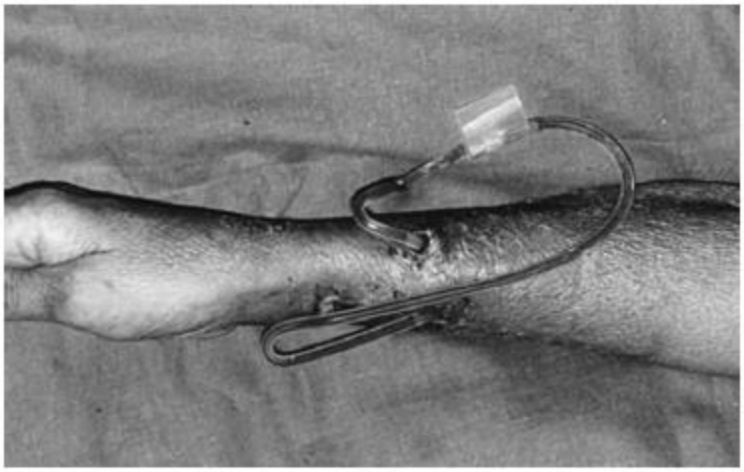


Figure 5–2 Scribner shunt.

A few general rules relate to the planning of vascular access-

- Arm vessels should be used in preference to the legs, and the nondominant arm should be used first. The latter rule is especially important in patients who needle their own fistula for home hemodialysis.
- Distal sites should be used first because this allows the greatest possible length of vascular conduit and preserves proximal sites for the future.
- When possible, the AVFs should be created preemptively.

The ideal AVF has the following features:

1. A blood flow of at least 300 mL/min
2. A large diameter, which facilitates venipuncture
3. Sufficient length to allow two dialysis needles to be inserted
4. Creation by a simple and quick operation, preferably LA
5. A good long-term patency rate

Autogenous Arteriovenous Fistulas

Wrist Arteriovenous Fistulas

- Originally a side-to-side, radial artery–to–cephalic vein AVF formed close to the wrist joint.
- The main variant, a side of artery–to–end of vein fistula, is preferred due to lower incidence of venous hypertension in the hand.
- Radiocephalic AVFs have a primary patency rate of approximately 80% at 2 years

Elbow Fistulas

1. BCF

- Many patients referred for vascular access have either inadequate forearm veins or a previously failed wrist fistula.
- Brachiocephalic AVFs probably are the best option when it is impossible to form a wrist fistula in either arm.
- The direct brachiocephalic AVF was first described by Cascardo and colleagues. Several technical variations of BCF are-
- The median cubital vein may be anastomosed directly to the brachial artery, and this technique has the advantage of arterializing the cephalic and the basilic venous systems.
- Alternatively, the deep perforating branch of the median cubital vein can be anastomosed to the brachial artery. BCF secondary cumulative patency rates ~ 80% at 3 years and 70% at 4 years.

2. ***BRACHIOBASILIC ARTERIOVENOUS FISTULAS WITH VEIN TRANSPOSITION***

Only a short section of the basilic vein at the elbow is superficial, and most of the vein is protected under the deep fascia. A much longer conduit can be created by dissecting the basilic vein from its bed and transposing it into a more convenient subcutaneous position down the middle of the upper arm.
The 1- and 2-year functional patency rates are ~ 50% to 80%

Graft Arteriovenous Fistulas-

- The graft material is tunneled subcutaneously between a suitable artery and vein and anastomosed to these using an end-to-side technique. The choice of graft material
- is between biological materials, such as autogenous long saphenous vein, and prosthetic materials, of which expanded PTFE is preferred.
- autogenous saphenous vein usage is limited by the variable quality of this vein With patency rates of 20% to 66% at 2 years.
- Expanded PTFE is easy to handle, of predictably high quality, and available in a wide range of sizes.
- The expected 2-year graft patency rate using expanded PTFE is ~ 60%.

Complications of Arteriovenous Fistulas and Graft Formation-

1. **Hemorrhage-**
    - If hemorrhage occurs in the first 24 hours postoperatively- due to a technical error with the anastomosis or a slipped ligature.
    - Late hemorrhage from an AVF can occur after venepuncture or as a complication of aneurysm formation and infection.

2. **Thrombosis**

    Although thrombosis may result from preoperative overdialysis leading to dehydration or intraoperative hypotension, a technical error should be suspected. Immediate re-exploration is indicated because it may be possible to salvage the situation by thrombectomy using a Fogarty catheter and subsequent refashioning of the anastomosis.

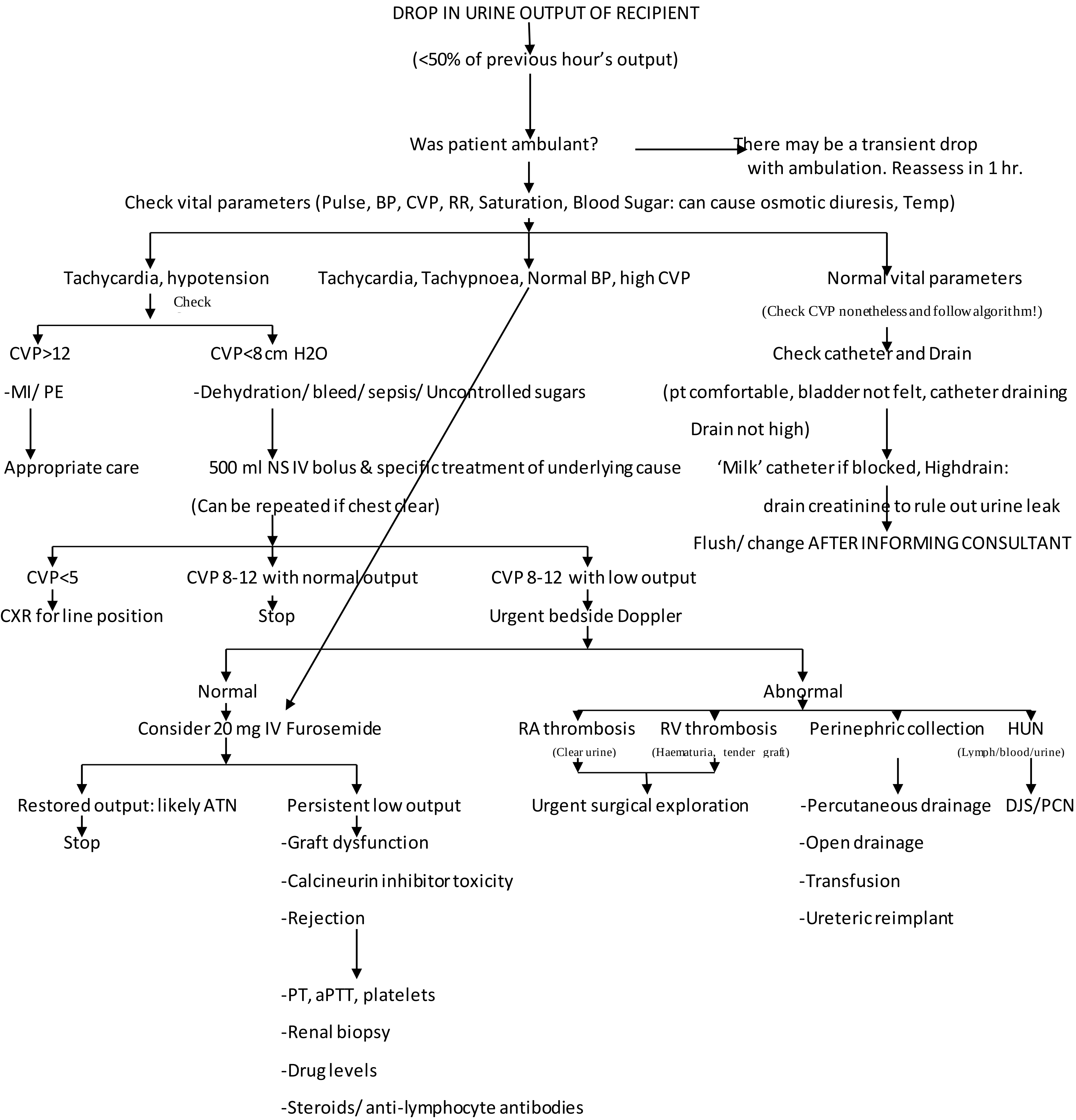
3. **Infection**

4. **Aneurysm Formation**

    The incidence is 10% for PTFE grafts compared with 2% for autogenous AVFs

5. **Vascular Steal Syndromes**
    - A vascular steal is diagnosed when there is hypoperfusion of the limb (usually the arm) distal to the arteriovenous anastomosis. This hypoperfusion occurs most commonly after procedures involving the brachial artery and in patients with generalized arteriosclerosis and diabetes.
    - Total fistula flow and steal can be limited by reducing the anastomotic length to 75% or less of the proximal arterial diameter; in most patients, this translates into an arteriotomy length of approximately 5 mm.

5. Immediate post transplant oligo/anuria (essay)


DROP IN URINE OUTPUT OF RECIPIENT
(<50% of previous hour's output)
Was patient ambulant?
There may be a transient drop with ambulation. Reassess in 1 hr.
Check vital parameters (Pulse, BP, CVP, RR, Saturation, Blood Sugar: can cause osmotic diuresis, Temp)
Tachycardia, hypotension
Check
Tachycardia, Tachypnoea, Normal BP, high CVP
Normal vital parameters
(Check CVP nonetheless and follow algorithm!)
CVP>12
-MI/ PE
Appropriate care
CVP<8 cm H2O
-Dehydration/ bleed/ sepsis/ Uncontrolled sugars
500 ml NS IV bolus & specific treatment of underlying cause
(Can be repeated if chest clear)
Check catheter and Drain
(pt comfortable, bladder not felt, catheter draining
Drain not high)
'Milk' catheter if blocked, Highdrain:
drain creatinine to rule out urine leak
Flush/ change AFTER INFORMING CONSULTANT
CVP<5
CXR for line position
CVP 8-12 with normal output
Stop
CVP 8-12 with low output
Urgent bedside Doppler
Normal
Consider 20 mg IV Furosemide
Restored output: likely ATN
Stop
Persistent low output
-Graft dysfunction
-Calcineurin inhibitor toxicity
-Rejection
-PT, aPTT, platelets
-Renal biopsy
-Drug levels
-Steroids/ anti-lymphocyte antibodies
Abnormal
RA thrombosis
(Clear urine)
RV thrombosis
(Haematuria, tender graft)
Urgent surgical exploration
Perinephric collection
-Percutaneous drainage
-Open drainage
-Transfusion
-Ureteric reimplant
HUN
(Lymph/blood/urine)
DJS/PCN

- The prompt diagnosis of rejection as the cause of allograft dysfunction is imperative to minimize irreversible damage to the kidney.
- Depending on the time from transplantation and the preceding level of renal function, the diagnosis can be obscure.
- Anuria / oliguria in a post transplant patient often indicates graft failure.

ETIOLOGY

The various causes for this could be analysed with regard to the **time since transplant**.

Oliguria/ anuria within 3 days :

1) Ureteric obstruction
2) Blood vessel thrombosis – Arterial / Venous
3) Hyperacute rejection
4) ATN .

Oliguria / anuria 3-7 days :

1) Acute rejection
2) Dysfunction of the graft
3) Cyclosporine induced nephrotoxicity
4) Acute interstitial nephritis
5) Surgical causes

Oliguria / anuria >7 days :

1) Chronic rejection
2) Drug related
3) Ureteric obstruction
4) Lymphocele

Early graft dysfunction can be due to infection, renal allograft rejection, urinary or vascular obstruction, cyclosporine or tacrolimus nephrotoxicity, Hyperglycemia, or Dehydration .

Rejection:

Hyperacute, Accelerated ACUTE rejection and Chronic rejection

Vascular complications :

Immediate vascular complications include

Kinking of the kidney graft's artery or vein, suture line stenosis, or thrombosis.

Thrombosis of the kidney graft may occur because of hyperacute rejection or thrombophilia.

Renal artery stenosis

Usually diagnosed because of hypertension that is progressively difficult to manage, with or without impaired renal function.

Renal Arterial thrombosis

Rare ***(less than 1%)*** complication that may occur as a result of

- Hyperacute Rejection,
- Postoperative Hypotension,
- Faulty technical performance of the anastomosis,
- Trauma to the intima of the donor artery during harvesting or perfusion,
- Severe atherosclerosis in the recipient vessels
- Wide disparity in the calibers of the donor and recipient vessels.
- Cyclosporine Toxicity (some cases)

Renal vein thrombosis

Rare (less than 1%) complication.

It may result from

- Technical error in performing the venous anastomosis,
- Ipsilateral femoro iliac thrombosis,
- External compression of the iliac or renal vein by perinephric fluid collection, or compression of the right common iliac vein between the right common iliac artery or aorta and the sacral promontory ***(silent iliac compression syndrome).***

SUSPECT-- Oliguria, graft enlargement, heavy proteinuria, and ipsilateral lower extremity edema.

Ureteral Obstruction :

- Generally a late complication of renal transplantation.
- Incidence has ***decreased to less than 5% to 10%*** of renal allograft recipients
- Still accounts for up to one-third of all significant urologic complications..

Diagnosis

- Azotemia in an otherwise asymptomatic patient
- Ultrasonography -- Hydronephrosis.
- If renal function is adequate, intravenous urography may allow delineation of the site of obstruction .
- Retrograde pyelography may be attempted to define the site of obstruction, (Difficulty in cannulation of the neoureteral orifice)
- Percutaneous nephrostomy placement with antegrade pyelography. Provides information on renal function
- Antegrade pressure / perfusion studies may also be of benefit in select cases.

The most common problem is distal obstruction that involves the ureteroneocystostomy.

Less common causes of ureteral obstruction include

- Extrinsic compression by hematoma, lymphocele or abscess
- Ureteral kinking
- Unrecognized intrinsic ureteropelvic junction obstruction.
- Rarely, intermittent obstruction -- ***Placement of the ureteral anastomosis in the mobile anterior dome of the bladder.***

TREATMENT:

- Definitive operative reconstruction of transplant ureter obstruction is dependent on the etiology and site of obstruction.
- Obstruction is limited to the very distal ureter, a ***repeat Ureteroneocystostomy***
- Intraoperative placement of a soft, self-retaining internal stent that is left indwelling for 4 to 6 weeks
- For extensive ureteral involvement -- ***Native ureter for a ureteropyelostomy to the transplant renal pelvis .***

- When the native ureter is used, the proximal native ureter can generally be ligated and the native kidney left *in situ*).
- In the presence of infection, native nephrectomy
- Anastomosis of the native ureter in a side-to-side fashion to the transplant renal pelvis . This precludes the possibility of a late complication associated with simple ligation of that ureter.
- Internal stent is left indwelling during the early postoperative period.

Salvage reconstructive procedures

- When the native ureter is not available or is otherwise inappropriate for use
- ***Vesicopyelostomy with or without a bladder flap*** .
- An ***ileal interposition.***
- ***Native ureterocalicostomy or vesicocalicostomy. -*** Transplant renal pelvis cannot be accessed either because of peripelvic fibrosis or an intrarenal anatomy-

MINIMAL INVASIVE

- Percutaneous nephrostomy drainage with ***transluminal ureteral dilation or endoscopic incisional ureterotomy***.
    - Short, discrete strictures limited to the distal ureter or ureterovesical anastomosis itself .
- Unrecognized intrinsic ureteropelvic junction obstruction in the donor organ -- ***Percutaneous endopyelotomy*** .

6. Management of post-transplant ureteric stricture

Stenosis and leakage of the transplant ureter occur in about 5% of recipients
Ureteral necrosis is a rare event (0.5%)

Risk factors-

- Non-adherence to preservation of the so-called “golden triangle,” encompassing the peripelvic and upper ureteral fatty tissue.
- Donor age >65 years is an independent risk factor for ureteral stenosis
- Transplants with more than two arteries, showed more frequent ureteral stenosis
- The longer the transport time (cold ischemic time [CIT]

Management-

Immediate Management-

- Internal or external (percutaneous) stenting is usually a short-term solution to overcome the immediate problem of renal insufficiency due to ureteral obstruction.

- For surgical therapy of transplant ureteral stenosis, the least invasive method is dilation of the stenosis using a retrograde (via cystoscopy) or antegrade (via percutaneous nephrostomy) technique. If done within 3 months postoperatively was more successful than later dilation.

Endosurgery via antegrade or retrograde access has been described-

- Using electrocautery
- HoYag laser ureterotomy
- Acucise ureterotomy

Open reoperation-

- Reimplantation of the stenotic ureter (after excising the stenotic part)
- Pyeloureterostomy between the donor renal pelvis and recipient ureter
- The recipient urinary bladder can be useful to reconstruct urinary drainage. Successful elongation of the bladder with a Boari flap/psoas hitch technique and also a direct connection of the transplant renal pelvis to the bladder (vesicopyelostomy).
- If the distance between the urinary bladder and the kidney is too large or if the recipient's ureter is not usable, ureteral replacement with ileum can be performed.
- As a salvage treatment, one can interpose an artificial ureter: Detour® tube with an inner layer of silicone and an outer layer of polytetrafluoroethylene.

7. Marginal donor

8. Management of post transplant lymphocoele

Lymphatic collections are usually found medial to the renal allograft
May occur in 36% of transplants

ETIOLOGY :
Arises from the lymphatics surrounding the iliac vessels that are divided during mobilization or Renal hilar lymphatics of the donor kidney.

PRESENTATION :
Produce pain, Ureteral obstruction, Voiding symptoms,
Renal or iliac vein compression leading to deep vein thrombosis or leg swelling.

DIAGNOSIS :
Ultrasound examination and Aspiration of the fluid using sterile technique.
Lymphatic fluid is usually clear with a high lymphocyte count, high protein content, and creatinine concentration similar to that of serum.

TREATMENT :

- Small, asymptomatic lymphoceles do not require treatment.
- Aspiration alone may resolve the problem, but repeated aspiration is discouraged because it may lead to infection and rarely results in permanent decompression.
- Percutaneous closed-system catheter drainage with instillation of sclerosing agents, such as ***povidone iodine (Betadine) or fibrin glue***
- Marsupialization in to the peritoneal cavity.
  - Best for Loculated lymphoceles, collections adjacent to the renal hilum, and those that are inaccessible for safe puncture
  - Laparoscopic or open surgical approach

- The transplant ureter, which is often incorporated into the wall of the lymphocele must be identified and carefully preserved.
- The peritoneal opening must be large enough to prevent bowel herniation.
- Cystoscopically placed stent in transplant ureter useful
- Omentum is usually placed in the opening to prevent closure.

PREVENTION :

- Reduced by minimizing the pelvic dissection and ligating lymphatics.
- ***Avoiding the immunosuppressant agent sirolimus*** in early postoperative period
- Placing a drain at the end of the procedure and leaving it for the initial postoperative course (FOR INSTILLATION OF SCLEROSANT)

9. Evaluation of live donor and pathophysiology of chronic rejection (essay)

- **Surgical goals**
  - Minimize warm ischemia time
  - Preserve renal vessels
  - Preserve ureteral blood supply
  - In the deceased donor, it is also necessary to obtain histocompatibility specimens

Amsterdam Criteria- LIVING KIDNEY DONOR : 7 POINTS

- Healthy volunteer
- No renal disease
- Low probability of getting renal disease
- No disease transmission to recipient
- Anatomically useable kidney
- Better kidney stays with donor
- Low surgical risk to donor

PRINCIPLES OF DONOR EXCLUSION

- Risk of abnormal renal function after donation – Familial renal disease, Obesity, Hypertension, Urolithiasis, Diabetes mellitus.
- High risk of preoperative mortality
- Transmission of cancer
- Coercion (involuntary donation)
- Underage
- Unsuitable anatomy

Exclusion criteria-

Absolute contraindications

- Age < 18 years
- Uncontrolled hypertension
- Diabetes mellitus
- Proteinuria (> 300 mg/24 h)
- Abnormal GFR for age
- Microscopic haematuria
- High risk of thromboembolism
- Medically significant illness (chronic lung disease, recent malignant tumour, heart disease)
- History of bilateral kidney stones
- HIV positive

Relative contraindications

- Active chronic infection (e.g. tuberculosis, hepatitis B/C, parasites)
- Obesity
- Psychiatric disorders

This is long but important if ESSAY-

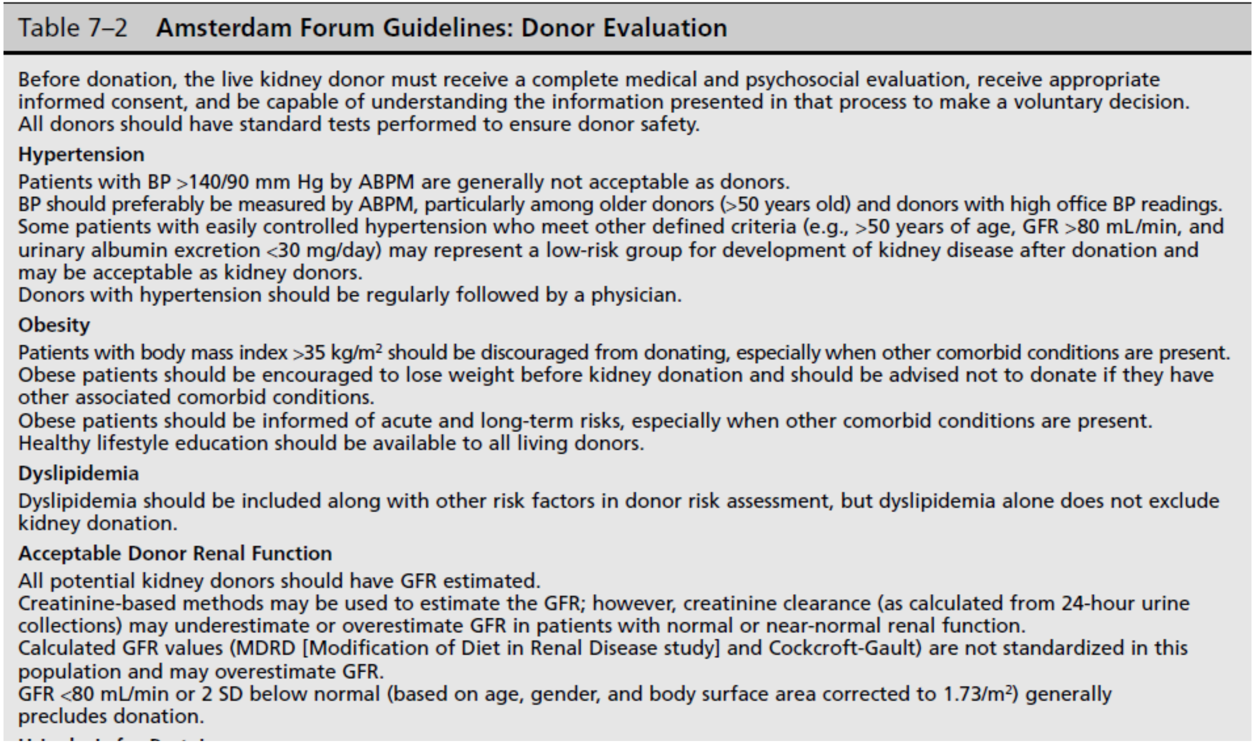


Table 7–2 **Amsterdam Forum Guidelines: Donor Evaluation**

Before donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision.
All donors should have standard tests performed to ensure donor safety.

Hypertension

Patients with BP >140/90 mm Hg by ABPM are generally not acceptable as donors.
BP should preferably be measured by ABPM, particularly among older donors (>50 years old) and donors with high office BP readings.
Some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, GFR >80 mL/min, and urinary albumin excretion <30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
Donors with hypertension should be regularly followed by a physician.

Obesity

Patients with body mass index >35 kg/m^2 should be discouraged from donating, especially when other comorbid conditions are present.
Obese patients should be encouraged to lose weight before kidney donation and should be advised not to donate if they have other associated comorbid conditions.
Obese patients should be informed of acute and long-term risks, especially when other comorbid conditions are present.
Healthy lifestyle education should be available to all living donors.

Dyslipidemia

Dyslipidemia should be included along with other risk factors in donor risk assessment, but dyslipidemia alone does not exclude kidney donation.

Acceptable Donor Renal Function

All potential kidney donors should have GFR estimated.
Creatinine-based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-hour urine collections) may underestimate or overestimate GFR in patients with normal or near-normal renal function.
Calculated GFR values (MDRD [Modification of Diet in Renal Disease study] and Cockcroft-Gault) are not standardized in this population and may overestimate GFR.
GFR <80 mL/min or 2 SD below normal (based on age, gender, and body surface area corrected to $1.73/m^2$) generally precludes donation.

Urinalysis for Protein

A 24-hour urine protein >300 mg is a contraindication to donation.
Microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

Urinalysis for Blood

Patients with persistent microscopic hematuria should not be considered for kidney donation unless urine cytology and a complete urologic workup are performed.
If urological malignancy and stone disease are excluded, a kidney biopsy may be indicated to rule out glomerular pathology such as IgA nephropathy.

Diabetes

Individuals with a history of diabetes or fasting blood glucose ≥126 mg/dL (≥7 mmol/L) on at least two occasions (or 2-hour glucose with oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) should not donate.

Stone Disease

- An asymptomatic potential donor with history of a single stone may be suitable for kidney donation if
  - No hypercalcuria, hyperuricemia, or metabolic acidosis
  - No cystinuria or hyperoxaluria
  - No urinary tract infection
  - Multiple stones or nephrocalcinosis are not evident on CT
- An asymptomatic potential donor with a current single stone may be suitable if
  - The donor meets the criteria shown previously for single stone formers and current stone <1.5 cm, or potentially removable during the transplant
- Stone formers who should not donate are those with
  - Nephrocalcinosis on x-ray or bilateral stone disease
  - Stone types with high recurrence rates and are difficult to prevent (see text)

Stone types with high recurrence rates and are difficult to prevent (see text)

Malignancy

- Prior history of the following malignancies usually excludes live kidney donation
  - Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer, and monoclonal gammopathy
- Prior history of malignancy may be acceptable for donation only if
  - Prior treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for end-stage renal disease
  - Prior treatment of malignancy does not increase the operative risk of nephrectomy
- A prior history of malignancy usually excludes live kidney donation, but may be acceptable if
  - Specific cancer is curable, and potential transmission of cancer can reasonably be excluded

Urinary Tract Infections

Donor urine should be sterile before donation; asymptomatic bacteriuria should be treated before donation.
Pyuria or hematuria at the proposed time of donation is a contraindication to donation.
Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer; urinary tuberculosis and cancer are contraindications to donation.

Live Unrelated Donors

Current available data suggest no restriction of live kidney donation based on the absence of an HLA match.
An unrelated donor transplant is equally successful to the outcome achieved by a genetically related family member, such as a parent, child, or sibling, who is not HLA identical to the recipient.

Determination of Cardiovascular Risk

- Clinical predictors of an increased perioperative cardiovascular risk (for noncardiac surgery) by the American College of Cardiology/American Heart Association standards fall into three categories: major, intermediate, minor
  - All major predictors—unstable coronary syndromes, decompensated heart failure, significant arrhythmias, and severe valvular disease—are contraindications to live kidney donation
  - Most intermediate predictors—mild angina, previous myocardial infarction, compensated or prior heart failure, and diabetes mellitus—are contraindications to donation
  - Minor predictors—older age, abnormal ECG, rhythm other than sinus, low cardiac functional capacity, history of stroke, and uncontrolled hypertension—warrant individual consideration

Assessment of Pulmonary Issues

Careful history and physical examination are the most important parts of assessing risk.
Routine preoperative pulmonary function testing is not warranted for potential live kidney donors, unless there is an associated risk factor, such as chronic lung disease.
Increased risk of postoperative pulmonary complication is associated with FEV_1 <70% or FVC <70% of predicted, or a ratio of FEV_1/FVC <65%.

Smoking Cessation and Alcohol Abstinence

Smoking cessation at least 4 wk before donation is advised based on recommendations for patients undergoing elective surgical procedures.
Alcohol should be avoided for a minimum of 4 wk to decrease the known risk of postoperative morbidity.
Cessation of alcohol abuse defined by DSM-III (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*): 60 g of alcohol/day sustained over >6 months

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CT, computed tomography; ECG, electrocardiogram; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GFR, glomerular filtration rate; HLA, human leukocyte antigen.

Pathophysiology of Chronic rejection-
Chronic allograft nephropathy, characterized by progressive renal dysfunction accompanied by chronic interstitial fibrosis, tubular atrophy, vascular occlusive changes, and glomerulosclerosis,

The Banff classification of chronic allograft nephropathy into two subtypes.

1. Chronic allograft nephropathy - type a
A nonspecific fibrotic ("sclerosing") subtype is characterized predominantly by tubular atrophy and chronic interstitial fibrosis). This is the more commonsubtype, but is etiologically nonspecific.
2. Chronic allograft nephropathy - type b
Characterized by additional glomerular and vascular features suggestive of immune-mediated chronic rejection, including glomerular capillary double contours and increased mesangial matrix (typified by transplant glomerulopathy) or fibrointimal hyperplasia in small muscular arteries (associated with intimal mononuclear cell infiltration, neointimal formation, or internal elastic lamina disruption
The central histological abnormality defining chronic allograft nephropathy is the presence of chronic interstitial fibrosis and tubular atrophy.

Graded by the extent of the tubulointerstitial damage as follows:

- grade I—mild 6% to 25% of the cortical area;
- grade II— moderate, 26% to 50% of the cortical area;
- grade III—severe, > 50% of the cortical area.

PATHOPHYSIOLOGY OF ALLOGRAFT DAMAGE.

Chronic Rejection
True chronic rejection may be relevant, however, in the modern era with immunologically active or noncompliant recipients;

- with excessive prescribed reductions of immunosuppressive therapy (e.g., following the diagnosis of cancer or late infection)
- when chronic low-level alloimmune activity is histologically manifested by persistent cellular interstitial inflammation and fibrointimal hyperplasia
- with transplant glomerulopathy associated with circulating donor-specific antibody and tissue C4d.

Input-Stress Model
Consists of series of immune and nonimmune stresses-

- including cellular infiltration;
- antibody-mediated alloimmunity
- nonimmune ("load") mechanisms, including hypertension, hyperfiltration,
- proteinuria, dyslipidemia, nephrotoxic drugs, and infection.

These stressors have been postulated to drive cells from a normal state into a senescent phenotype, exhaust repair processes, and deplete the finite nephron supply, leading tograft failure.

Cumulative Damage Hypothesis
chronic allograft nephropathy is the end result of a series of time-dependent immune and nonimmune insults inflicted on the transplanted kidney, resulting in permanent nephron damage.

Others-

- Pathophysiological Stressors
- Failure to Resolve Chronic Inflammation
- Epithelial-Mesenchymal Transition–Induced Fibrosis
- Replicative Senescence
- Cortical Ischemia
- Internal Architectural Degradation

10. Steroid free immunosupression regime

Steroids have been a part of any immunosuppressive regimen since the beginning of kidney transplantation because of their anti-inflammatory and immunosuppressive property, in addition to their ability to reverse acute rejection.
However long-term use of steroids had adverse effects like-

- worsening hypertension
- worsening dyslipidemia
- new-onset diabetes
- osteoporosis
- avascular necrosis
- susceptibility to infection

Modern immunosuppressive regimens have made rapid steroid discontinuation more feasible than previous immunosuppression regimens, especially with the introduction of mycophenolic acid (MPA) therapy.

1. AN early RCT showed that steroid withdrawal at 4 days post-transplant resulted in a similar incidence of rejection compared to standard steroids at 6 months in renal transplant patients receiving cyclosporine (CsA), mycophenolate mofetil (MMF) and basiliximab.
2. In another prospective study, a single perioperative dose of methylprednisolone with tacrolimus, MMF and daclizumab was given, the efficacy was similar to that seen with standard steroids: the biopsy-proven acute rejection (BPAR) rate was ~16%% in both arms.
3. FREEDOM Trial (A Randomized, Multicenter Study of Steroid Avoidance, Early Steroid Withdrawal or Standard Steroid Therapy in Kidney Transplant Recipients)
    - These results indicate that in renal transplant patients receiving CsA-M (CsA microemulsion), enteric-coated mycophenolate sodium (EC-MPS) and steroids with basiliximab induction, steroid withdrawal at day 7 post-transplant achieves comparable 1-year renal function to a standard steroids regimen,.

    - One-year graft and patient survival rates were similar, although the proportion of patients experiencing biopsy-proven acute rejection (BPAR) following early steroid withdrawal was 10% higher than in the standard steroids group.
    - At 12 months, 65 patients (~60%) randomized to steroid-free therapy and 82 patients (70%) in the steroid-withdrawal group were free of steroids.